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CEREBRAL VASCULAR LESIONS AND THE TENTORIAL PRESSURE CONE

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HERNIATION through the incisura tentorii as the result of increased intracranial pressure has been emphasized recently by several observers, notably Geoffrey Jefferson (1938) and Moore and Stern (1938), as the anatomical basis for some organic nervous symptoms. This lesion is generally regarded as being especially prone to occur with abscesses involving the temporal lobe, but it has been noted in association with tumours of this region and of other parts of the brain. The present case is an example of such a herniation in which the structural changes have been especially studied, and in particular the altered relations of the posterior cerebral artery to the edge of the tentorium cerebelli.

Case Report

CLINICAL HISTORY

The patient, Kathleen B., was a child of ten years. The previous history contained nothing of note. Early in the month of September, 1938, the parents noticed she was becoming dull and listless. She was taken to a Welfare Centre but no definite conclusions were reached as to the cause of this change. On September 27th acute symptoms presented themselves in the form of intense headache and repeated vomiting. On the third day the parents took the child to the Belfast Hospital for Sick Children. On examination it was found that there was marked head retraction, a positive Kernig's sign and other evidence of meningeal irritation. Lumbar puncture was performed and the fluid was found to be turbid and under pressure. Protein was slightly increased (0.06 per cent.) and there were 500 cells (lymphocytes) per cm. The sugar and chloride content was normal. Culture was sterile and the Wassermann reaction negative. Admission to hospital was urged but the parents refused.

An interval of 18 days elapsed. The child apparently improved to some extent,

but on the 18th November the parents brought her back to hospital and she was admitted under the care of Dr. F. M. B. Allen. The clinical condition was then similar to that found at the previous examination with the addition, however, that the pupils were now unequal, the left being larger than the right. The cerebro-spinal fluid was still under pressure but contained only 40 lymphocytes per cm. Congestion and swelling of the optic discs were observed, especially on the left side. The child exhibited noisy behaviour and great motor restlessness so that accurate observation was difficult. The following day she had a seizure, consciousness being lost and clonic convulsive movements occurring in the right arm and leg. After the fit the patient remained in a comatose state for twenty-four hours. When consciousness was regained she complained of pain in the left ear. The temperature, which had been normal, rose to 102° F. Aural examination showed nothing definite. There was neither tenderness nor swelling over the mastoid process, but after consultation Mr. D. H. Craig exposed the middle ear and mastoid. The bony cortex was sclerotic, but beneath it, pus was found under pressure and there was a cholesteatomatous mass which was eroding the tegmen. The middle and posterior fossæ were exposed but the dura was found to be healthy. The general condition of the patient was so poor as to make further steps hazardous and the operation was concluded. The pus removed was cultured and gave a profuse growth of the staphylococcus aureus.

Following operation, the child remained semicomatose, but by the 26th November she had sufficiently improved to co-operate on examination. It was then apparent that she was blind, neither hand movements nor light being appreciated and the pupils remaining dilated and fixed. At this time the left plantar reflex was found to be extensor, but subsequently and until the time of her death both plantars were flexor. One of us (R. S. A.) was invited to see her on the 30th November. The abnormal signs observed then were as follows :

Psychic functions: The patient lay quietly on her side repeating over and over again: " Will you tell my daddy, please, my daddy please," she was able to understand what was said to her and reply correctly and could carry out simple requests. When given objects such as a hair brush, or when a pair of scissors was placed in her hand, she showed by gesture that she understood what they were. But when asked to name them she replied, " I know . . . a . . . a . . .". Mentioning the name of the object immediately secured her recognition.

Cranial nerves: Papilloedema was present, most marked on the left side. The presence of some bilateral secondary optic atrophy suggested that the condition had been present for some time. The pupils were dilated, immobile and unequal, and the left greater than the right. Upward movements of the eye were deficient on the left side but otherwise the ocular movements were full and there was no nystagmus. The right naso-labial fold was indistinct and weakness of the lower part of the right face was evident on voluntary and involuntary movements.

Reflexes: The abdominal reflexes were absent on the right side. The plantar reflexes were flexor in type. The knee and ankle jerks could not be obtained.

There was no obvious loss of power except in the face. Co-ordination was good and no sensory changes were observed. The signs of meningeal irritation formerly observed had disappeared. A diagnosis of temporal lobe abscess was made and craniotomy advised, but the patient became steadily worse, and coma and death supervened some days later.

Post-Mortem Findings

A post mortem examination was conducted within two hours of death. Permission was granted only to examine the cranial contents. The operation wound behind the left ear was discharging a little pus. On removal of the

calvarium the dura was found taut and adherent to the underlying brain over the left temporal region. There were no organized thrombi in the cortical veins nor in the great venous sinuses. No abscess was found between the dura and the roof of the left middle ear. The left middle ear and the mastoid air cells contained only a small quantity of pus. The other air sinuses and the pituitary fossa were normal. No exudate was found over the base of the brain and no appreciable thickening of the membranes.

Over the left mid-temporal gyrus a pale yellowish grey area was seen which felt soft and fluctuant. On the medial aspect of the occipital lobe the cortex

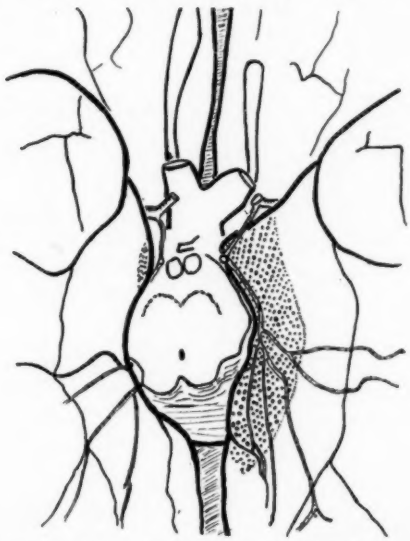

Fig. 1.—A line drawing traced over a photograph of the inferior surface of the brain. The left posterior cerebral artery is displaced on to the inferior aspect of the brain. Its branches may be pressed upon by the edge of the tentorium cerebelli or the vessel may be stretched or its branches kinked. The herniated area is dotted. Note the increase of the inferior surface medial to the collateral fissure.

above the calcarine fissure was shrunken and slightly yellow in colour. Below the fissure it was congested, slightly swollen and showed multiple petechial hæmorrhages. These changes did not extend to the tip of the occipital pole nor to the lateral aspect. The right occipital lobe was normal. The mid-line structures were noticeably displaced towards the right. The left uncus was clearly seen, the left hippocampal gyrus being grooved by the tentorial edge (Fig. 1). The posterior cerebral artery was stretched by the prolapsed gyri and lay in the hippocampal sulcus on its medial margin. The line of the tentorial edge crossed the course of the artery only in the extreme posterior part of its course and there was no evidence of thrombosis of the vessel or of its branches. On the right side the tentorium cerebelli had produced a tiny notch on the medial margin of the hippocampal gyrus where it turned round into the uncus. Owing to displacement of the brain to the right, the mid-brain at the level of the third cranial nerve had been deeply grooved on its lateral aspect by the right free margin of the tentorium cerebelli (Fig. 2). At this level the fourth cranial nerve swept round to the ventral aspect of the brain. There

was very slight moulding of the medulla and of the cerebellar tonsils by the foramen magnum.

On section of the brain after fixation a large irregular shaped abscess was found occupying the greater part of the left temporal lobe (Fig. 3). This had extended forwards to within one inch of the anterior tip of the temporal lobe. More medially, another prolongation reached the posterior part of the lentiform nucleus and the œdematous wall came into relation with the more postero-lateral and inferior part of the internal capsule. The medial wall of the abscess cavity was formed by the ependyma of the occluded inferior horn of the lateral ventricle. It was thus closely applied to the hippocampus and to the thrombosed

Fig. 2.—This shows the grooving of the right (contralateral) peduncle by the edge of the tentorium cerebelli. The cranial nerves are numbered.

choroid plexus of the inferior horn. A part of the uncus and of the hippocampal gyrus had been driven downwards through the incisura tentorii (Fig. 4). Posteriorly, about the level of the splenium, this abscess communicated with a thicker walled abscess which extended almost to the surface of the mid-temporal lobe and as far back as the upper limb of the mid-temporal sulcus. In addition to the two infarcts of different age in the occipital cortex there was a recent area of softening with areas of hæmorrhage in the intero-lateral part of the thalamus. In the prolapsed uncus of the left side there was a well marked band of hæmorrhage beneath the grey matter. There were a few small areas of softening and hæmorrhage in the mid-brain on the right side.

A staphylococcus aureus was isolated from the left ear, the temporal lobe abscess and from a post-mortem specimen of the cerebro-spinal fluid.

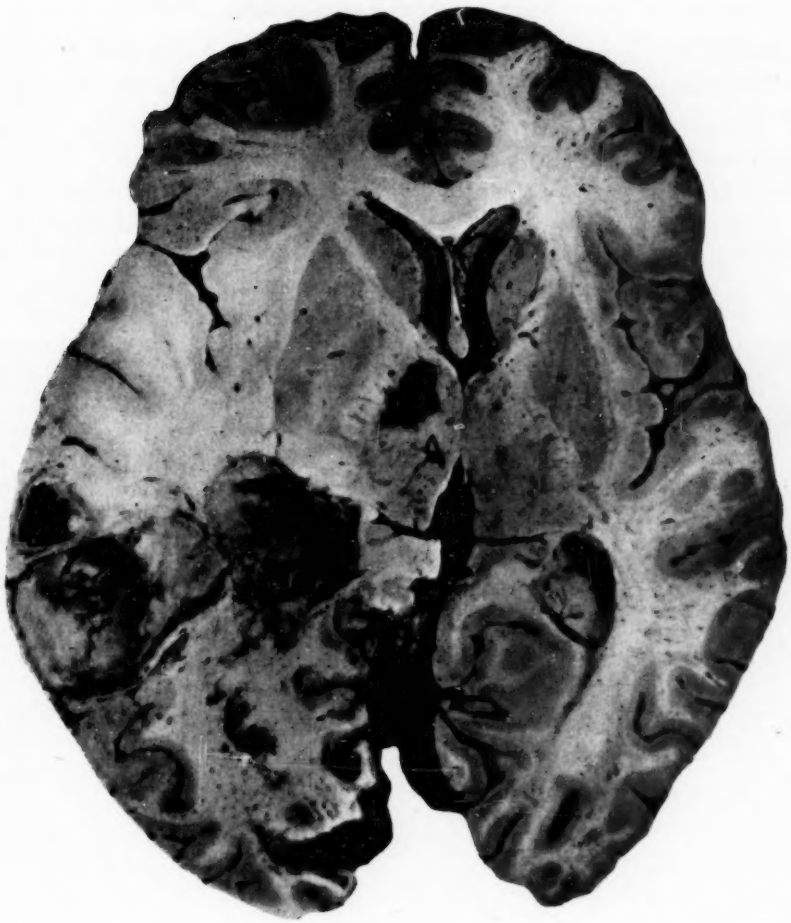

Fig. 3.—Section of the brain showing part of the abscess, the occipital infarct below the calcarine fissure and the thalamic infarct.

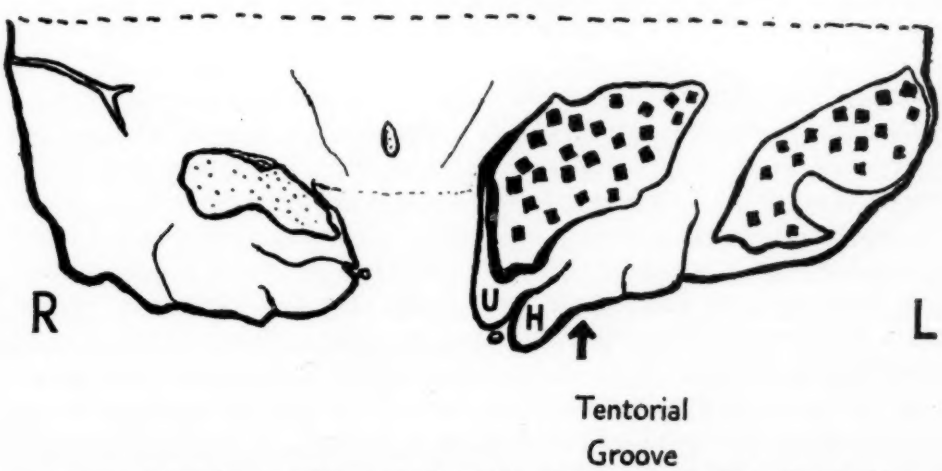

Fig. 4.—A line drawing of sections of brain showing tentorial groove and part of the uncas (U) and of the hippocampal gyrus (H) pressed downwards.

Microscopical Examination

Sections of the temporal bone showed considerable fibroblastic proliferation and the inflammatory lesion was regressive. The pituitary was normal. The walls of the abscess were formed by granulation tissue infiltrated by plasma cells and lymphocytes. The capillary endothelial cells were swollen. Outside this there was evidence of considerable glial proliferation. Mononuclear cells, chiefly lymphocytes were present in some excess in the perivascular spaces and in the overlying subarachnoid space. Sections from the left occipital lobe in the area above the calcarine fissure showed the cortical grey matter, more

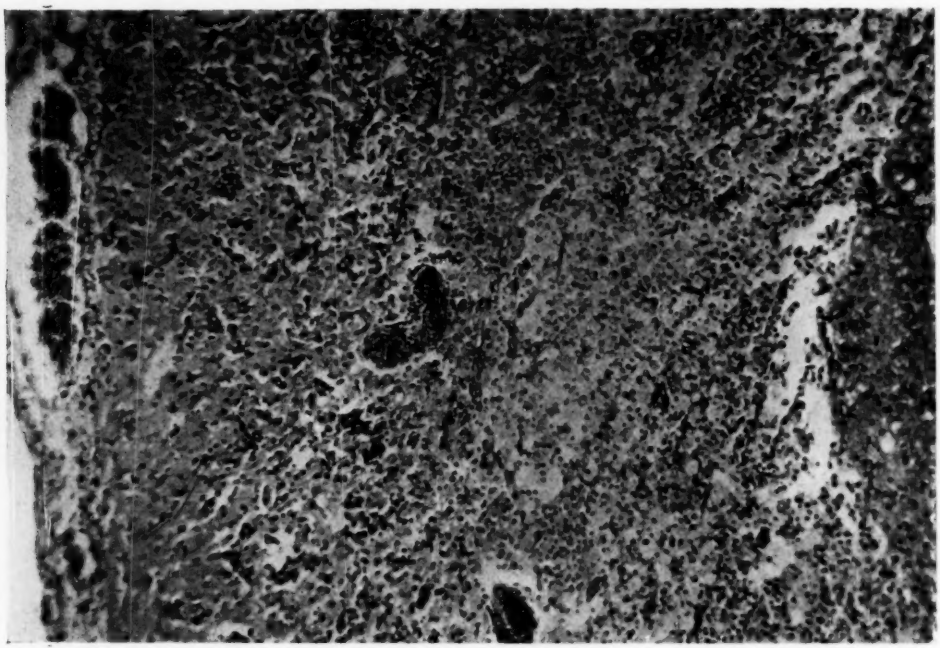

Fig. 5.—The cortex above the calcarine fissure. Fat engorged compound granular corpuscles, proliferation of microglia, and swelling of the capillary endothelial cells are most marked in the deeper layers.

especially in the deeper laminæ, in the process of removal by compound granular corpuscles. These were gorged with fat. Astrocytes were proliferating. The blood-vessels were very prominent and the capillary endothelial cells greatly swollen (Fig. 5). In the lingual gyrus the changes were much more recent. The capillary endothelium was swollen and from many capillaries red blood cells had escaped. Sometimes there were small aggregates of polymorphonuclear leucocytes, but glial reaction was absent (Fig. 6). Numerous sections across the left posterior cerebral artery and its branches showed no thrombosis and no structural change in the wall of even the smallest branches. The infarct in the thalamus was also of quite recent date. There was rupture of capillaries with escape of red blood cells and a few collections of polymorphonuclear leucocytes, but glial reaction was very slight. There was no inflammatory reaction in the adjacent ventricle or choroid plexus. The motor fibres of the

left side were but slightly affected in the region of the thalamic infarct. At a slightly lower level some fibres were involved by œdema and reactive change resulting from the recent thrombosis of the choroid plexus of the obliterated inferior horn of the lateral ventricle. This had involved more the inferior aspect of the corpus striatum and the structures of the posterior part of the internal capsule. There were a few areas of petechial hæmorrhage but no glial reaction as the fibres sweep downwards into the peduncles.

The ependyma of the inferior horn of the left ventricle was preserved in parts, but inflammatory reaction involved the ventricular aspect of the uncus and the hippocampus. The capillary endothelial cells were swollen and red blood cells

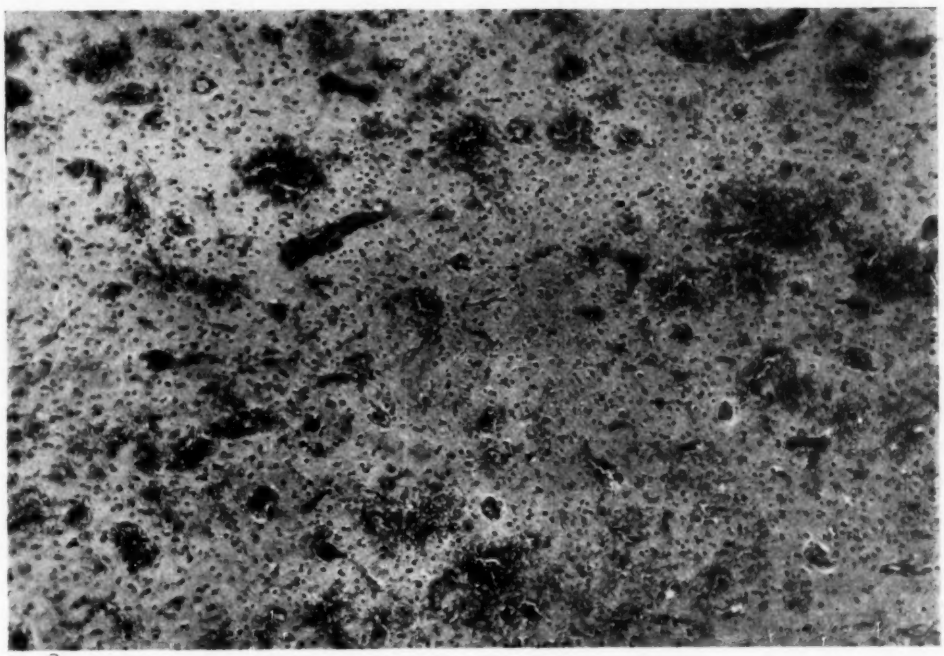

Fig. 6.—The cortex below the calcarine fissure. Glial reaction is absent, but there is some swelling of the endothelial cells of capillaries and an escape of red blood cells.

and sometimes polymorphonuclear leucocytes surrounded some of the capillaries. Microglial cells showed swelling and proliferation. There was no inflammation or vascular lesion in the underlying optic tract and only slight thickening of the pia and a few mononuclear inflammatory cells on the surface of the uncal and hippocampal gyri, and around the cerebral peduncles and midbrain. Nerve cells were slightly reduced in number in the left hippocampal gyrus. On both sides the grooving by the edge of the tentorium has resulted in a localized reduction of nerve cells with necrotic changes in some cell nuclei, and especially on the right side, some proliferation of the microglia.

Apart from slight œdema and congestion of vessels, sections through the corpora quadrigemina and the subthalamic nuclei presented no other lesion. The periaqueductal grey matter also appeared normal. Elsewhere in the midbrain the changes were confined to the right side. Where the peduncle was grooved by the tentorium cerebelli there was some œdema, axis cylinders being

swollen and tortuous, and there was slight proliferation of glial elements, chiefly of the microglia. The changes were not confined to the more superficial areas. There were also areas of necrosis with the bulbous ends of interrupted axis cylinders situated deeper within the peduncle. In areas in the tegmentum and red nucleus the venules and capillaries were congested and the endothelial lining cells prominent and there were small petechial hæmorrhages without glial reaction.

In the visual pathway the most marked change affected the fibres in front of the chiasma. Degeneration of myelin had occurred in the upper fibres of the right optic nerve and in a wedge-shaped area on the lateral aspect of the left. Behind the chiasma there was no significant loss of fibres. There was no demonstrable change in the third nerve nuclei or in the proximal part of the nerve. There was no degeneration in the fourth cranial nerve, either before or after it came into relation with the edge of the tentorium as it sweeps round the mid-brain.

Commentary

The main interest lies in the production of lesions in areas remote from the primary lesion by changes in their blood supply. While some of the demonstrable lesions are almost terminal, their distribution indicates those areas which must suffer the greatest functional disturbances by such an alteration of their blood supply. In the occipital lobe the area most affected is that above the calcarine fissure which is supplied by the calcarine and parieto-occipital twigs of the occipital branch of the posterior cerebral artery. In this case the posterior cerebral artery has been affected in its cortical rather than ganglionic distribution. Occlusion was probably only temporary and there was no change in the vessels themselves and no thrombi in their lumen. Moore and Stern (1938) also found no change in even the smallest arterioles. Not all branches were affected equally nor at the same time as the different ages of the infarcts show. Reflex vaso-motor constriction cannot be excluded but the distribution indicates that small arteries, rather than arterioles, must have been affected at the same period.

It is very readily assumed that the posterior cerebral artery in these cases is forced into contact with a free edge of the tentorium (Jefferson 1938, Moore & Stern 1938). A study of the relationship of the artery and of the tentorial groove (Fig. 1) suggests that while the artery is displaced on to the more exposed inferior surface of the brain by the stretching out of the uncal and hippocampal gyri, it is only in the more posterior part of the course that it comes into relation with the edge of the tentorium. Here, however, its termination, the occipital branch about to enter the calcarine fissure is no more exposed than the course of the anterior and middle temporal branches which are given off earlier. The areas supplied by these vessels were normal but may have been bĕtter nourished by anastomotic channels. It is also highly improbable that the ganglionic branches, apparently affected in some of Moore & Stern's cases, could be thus involved. Some degree of herniation of the uncus is not uncommon and in

examining uncomplicated cases the possibility that direct pressure by the tentorial edge could affect the vessel appears somewhat unlikely. Especially with rapidly progressive herniation the vessel or its branches may be stretched or distorted and branches kinked. This would result from their situation on the lateral aspect of the bulging uncus in the fissure between the uncal and hippocampal gyri when this carries them away from the mid-line and downwards through the incisura tentorii (Fig. 4). The vessels would readily stretch to accommodate themselves to their new course and might be expected to show no microscopical changes. The brain substance supplied would be irreparably damaged. The herniation affects those parts of the uncal and hippocampal gyri which normally lie just above and medial to the foramen. These are " rolled out " as the space filling lesion above drives them down through the incisura. The wider area of the affected side overlying the foramen results from the shift of the brain to the opposite side until the crus cerebri is notched by the opposite tentorial edge.

Following the classical account of Beevor (1908 and 1909), confirmed by Shellshear (1920), of the cerebral arterial supply, the area of thalamus involved is in great part supplied from the posterior communicating artery. Traction on the posterior communicating artery, and probably also, alterations in the course of this vessel owing to the shift of the hemisphere, as well as the local œdema of the brain surrounding the abscess may be considered as possible causes of this terminal infarction.

Shortly after the sudden apoplectiform seizure the child appeared completely blind and could neither appreciate light nor hand movements and the pupils were dilated and immobile. Complete testing of the visual fields was, therefore, quite impossible. There was some degree of optic atrophy superimposed on the papillœdema, but histological examination of the optic tracts confirmed the clinical opinion that this was insufficient to account for all the symptoms. The absence of lesions in the region of the optic thalamus, or in the right occipital radiation or lobe, suggest that in this child, at least an impression of complete blindness was created by the loss of the left visual cortex or its association tracts.

The involvement of the right crus cerebri, which clinically only produced a transient change in the left plantar reflex, and the terminal lesions in the right red nucleus resulted from the shifting of the axis of the brain bringing the crus against the edge of the tentorium (Kernohan and Woltman 1929). The lesions have resulted from pressure on vessels entering or emerging from the brain. Direct pressure to the right and left hippocampal cortex and to the surface of the right crus has only produced a very minor local effect.

Histologically there was no evidence of any lesion in the neighbourhood of the aqueduct or the third nerve nuclei and the proximal part of both nerves showed no demonstrable abnormality. The pupillary abnormalities probably resulted from pressure of the herniated uncus on the oculomotor nerve.

It is obvious that familiarity with the occurrence of tentorial herniation and the vascular changes taking place in the territory supplied by the posterior cerebral artery would be of assistance in assessing correctly some apparently

conflicting clinical signs. In the present case after the sudden apoplectiform seizure and the resulting blindness it was recognized that other lesions must be present as well as the abscess in the temporal lobe. Their nature was not recognized until after autopsy.

Summary

A case of temporal lobe abscess presenting many diagnostic difficulties is described.

Vascular lesions especially in the occipital lobe, resulted from herniation of the uncal and hippocampal gyri through the incisura tentorii. The possible mechanism of the vascular changes is discussed, and as the onset was sudden and no permanent arterial damage demonstrable, temporary occlusion by stretching and kinking of the posterior cerebral artery is considered as well as the possibility of direct pressure from the edge of the tentorium.

Recognition of the possibility of the condition may be of considerable clinical value in a correct localization of apparently conflicting clinical findings.

We wish to thank Professor J. H. Biggart for much valued help and advice.

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THE MECHANISM OF CONTRE-COUP INJURY

BY

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WHEN one considers the various types of intracranial lesion produced by trauma to the head—extradural hæmorrhage, subdural hæmorrhage, cortical laceration, hæmorrhage into brain substance or ventricles—there is one type of injury which of recent years has excited much speculation as to the mechanism of its causation, namely, " contre-coup injury."

It has long been observed in persons who have died as a result of trauma to the head and have come to autopsy that gross damage to brain tissue most frequently occurred, not in the situation immediately underlying the area of skull at which the traumatic force was applied, but rather at the pole of the brain diametrically opposite to the point struck. Thus, for example, a blow impinging on the skull in the region of the occiput might in some cases cause

Fig. 1.—Severe contre-coup traumatic cortical laceration and hæmorrhage of the right frontal pole following a blow in the left occipital region. In this case right craniotomy was performed prior to death and a certain amount of completely " pulped " brain tissue sucked out from frontal area—this being responsible for part of the actual defect seen.

some gross damage to the cortex of the brain immediately underlying the occiput, but the main cortical damage almost invariably would be sustained by the frontal and temporal poles diametrically opposite. Such is the injury referred to as contre-coup.

An illustration of a severe case of such contre-coup injury is given in Figs. 1 and 2. The arrow indicates the direction and area of application of the traumatic force.

Although contre-coup traumatic laceration is possible in head injuries in all planes, frontal contre-coup caused by occipital injuries, which is by far the most common and extensive, will be taken as a type for the purpose of this paper.

Fig. 2.—Horizontal section through the cerebral hemispheres cut through the area of contre-coup injury seen in Fig. 1. This shows the depth of the injury and the severe œdema of the right cerebral hemisphere.

If we consider a statistical analysis of the intracranial lesions found at autopsy in cases of traumatic head injury, we find figures such as the following: Martland and Beling (1929) reviewed 309 such cases, and found that of these 309 cases 177, or 57 per cent., showed contre-coup cortical laceration, while only 47, or 16 per cent., showed " direct " cortical laceration. In a small series of 33 cases reviewed at the Banting Institute, Toronto, 14 showed contre-coup cortical laceration. Such figures seem to indicate that contre-coup injury is the most constant finding in cases of severe traumatic injury to the head. Thus, contre-coup is not only interesting but important (Fig. 3).

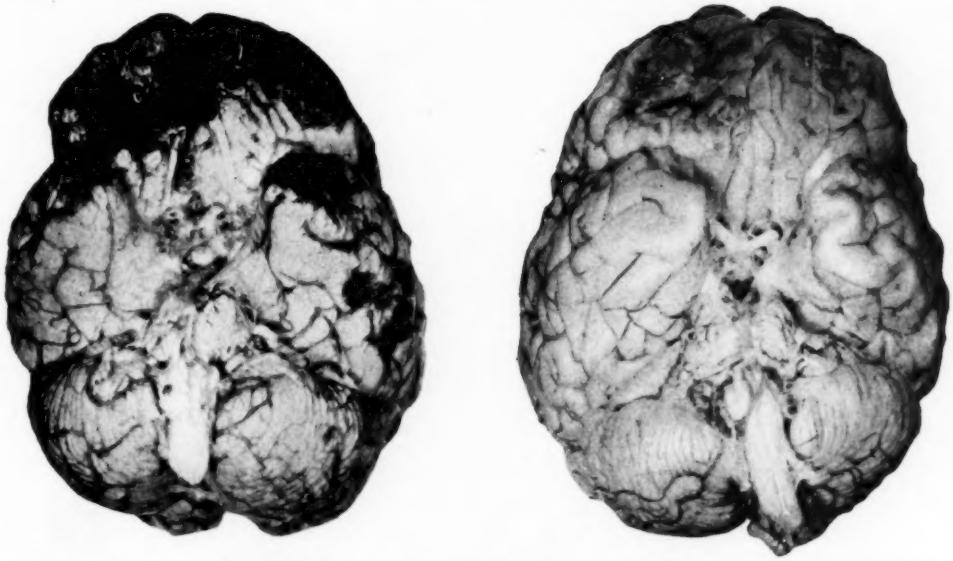


Fig. 3.—The bases of the brains of two patients, each of whom had received a blow on the left side of the back of the head. The brain on the left shows typical recent contre-coup damage of the frontal and temporal poles, more marked on the right. The old, healed contre-coup lesion seen in the brain on the right was the result of a blow which the patient received eight years before his death.

Anatomical and Pathological Considerations

Before going on to a discussion of how these contre-coup injuries might be produced, it is well to review a few anatomical and pathological features of importance, which are illustrated in Figs. 4 and 5.

The skull in which the brain is encased has several interesting features:

(*a*) It is composed of many separate bones, separated by suture lines which gradually fuse from youth to very old age to form a rigid brain case.

(*b*) The floor of this " brain case " is reinforced by thickenings and ridges of bone which might be considered as buttresses resisting deformation of skull (Fig. 4).

(*c*) The skull has various foramina, the most important of which are the foramen magnum and the jugular foramina situated rather posterior to the centre of the base of the skull (Fig. 4).

The various structures which envelop the brain within the skull must be considered: The tough dura mater separated by a film of synovial-like fluid

from the underlying more delicate arachnoid membrane which bounds the subarachnoid space in which cerebrospinal fluid circulates and from which the blood vessels of the brain enter its tissues. The arachnoid membrane is attached to the pia mater, a thin and delicate membrane adherent everywhere to the surface of the brain, by fibrous trabeculæ which traverse the subarachnoid

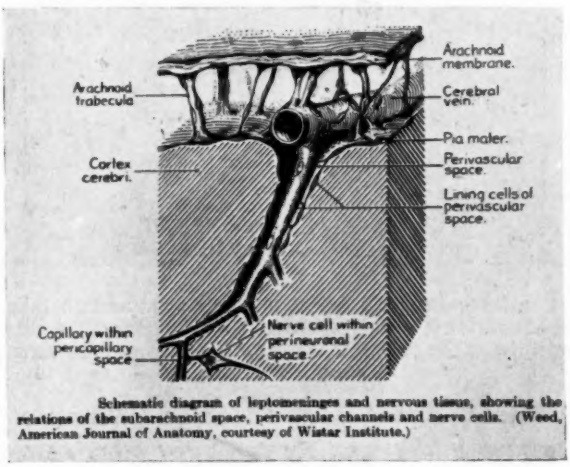
Fig. 4.—The right half of the base of the skull to show, in particular, the reinforcing bony buttresses.

space (Fig. 5). In the brain itself, we distinguish the cortex of the brain, with its large blood supply, from the underlying white matter, with its relatively less abundant blood supply.

When we consider the pathology of contre-coup injury we observe that it appears to be essentially a hæmorrhagic phenomenon. There is hæmorrhage

from the small blood vessels in the superficial layers of the cortex of the affected region of the brain. These may be merely " ring " or " streak " hæmorrhages into the Virchow-Robin spaces and capillary fields of the small vessels of the cortex, these hæmorrhages having a tendency to occur toward the summits of the convolutions. On the other hand, the hæmorrhage may be so severe that quite extensive areas of cortex are literally " torn to pieces " and converted into a bloody pulp, filling a cavity in the brain tissue which may extend quite deep into the underlying white matter (Fig. 2), and which is bounded by tissue showing the smaller hæmorrhages described and having a ragged and lacerated surface. The subarachnoid space is locally filled with extravasated blood and bits of avulsed brain tissue and the whole cerebrospinal fluid is rendered bloody. Such severe damage probably develops gradually by an oozing of blood from ruptured small vessels over some period of time.

In Fig. 6, drawn from a miscroscopical section of a case of contre-coup



Schematic diagram of leptomeninges and nervous tissue, showing the relations of the subarachnoid space, perivascular channels and nerve cells. (Weed, American Journal of Anatomy, courtesy of Wistar Institute.)

Fig. 5.—Schematic diagram of leptomeninges and nervous tissue, showing the relations of the subarachnoid space, perivascular channels and nerve-cells. (Weed, *American Journal of Anatomy*, courtesy of Wistar Institute.)

laceration, an attempt is made to illustrate graphically what we believe to be the essential lesion in contre-coup injury. It is meant to stress the idea, not universally accepted, that the primary hæmorrhage is intracortical.

Theories as to Mechanism by which Contre-coup Injury is Produced

On first being confronted with the fact of contre-coup injury, there is a tendency to seize upon one of the " simple explanations " given for its production and to accept it as the " cause " of the phenomenon. But when one stops to consider the many possible factors which may play a part in the production of contre-coup brain injury, the problem assumes very real complexity. It is intended here to discuss briefly these factors, and to present several new conceptions which make for interesting speculation.

Concerning the type of blow which causes contre-coup injury, we have little

to say except that, in our observation and in that of others, contre-coup is more liable to be produced by a " heavy " blow of some duration applied over a fairly large area of the skull than by a sharp blow to a small area which has a greater tendency to cause a depressed fracture of the skull. It would appear that falls and vehicular accidents, where the moving head is arrested by a large resistant object, are especially conducive to contre-coup injury. Much more

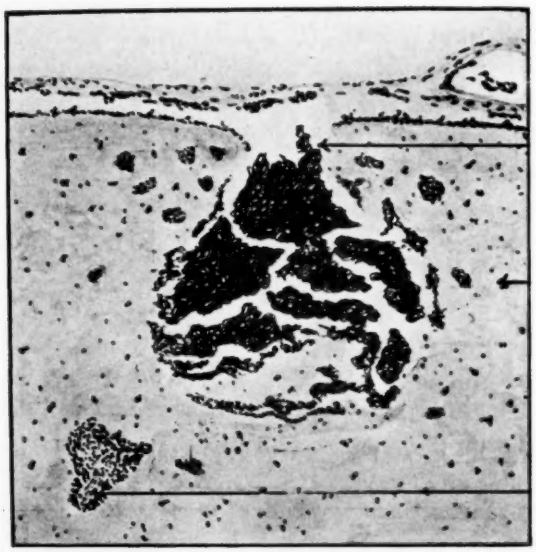


Fig. 6.—Drawing of a low-power view of a microscopical section taken from an area of contre-coup cortical laceration and hæmorrhage. The primary intracortical hæmorrhage is seen to have broken through the pia mater into the overlying subarachnoid space.

definite than this is the fact that blows on the occipital region are more liable to produce contre-coup injury than blows on any other part of the head.

But how does such a blow act upon the head to produce this contre-coup injury? Cassasa (1924) sought to explain the phenomena of concussion and cerebral contusion with production of " ring " hæmorrhages, which we have mentioned, mechanically by the forceful driving of cerebrospinal fluid from the subarachnoid space into the perivascular and perineural spaces (Fig. 5) This suggestion would enter into any consideration of the immediate cause of the pathological changes seen in cerebral contusions but it really does not bear on the problem of how the contre-coup phenomenon occurs.

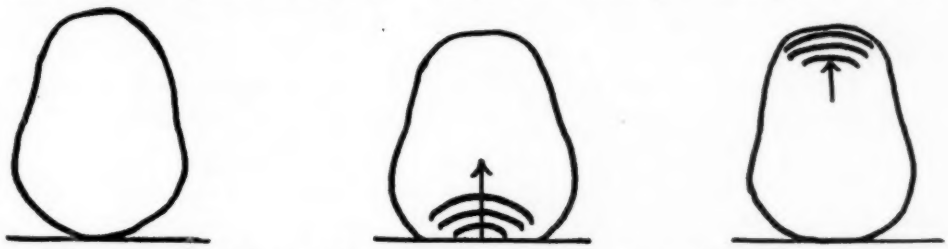
A. When the Skull is struck is it deformed, and if so, is this the Significant Factor?

A 1. We might first postulate a simple " compression wave " theory which states, with truth, that when a force is applied which acts for an extremely short time fluids are not entirely incompressible (witness the çonduction of sound by compression wave in water). Accordingly, when the skull is struck, the area struck is deformed or pushed inward on the underlying cortex (Fig. 7). Since this cortex is supported by other " compressible " nervous tissue beyond

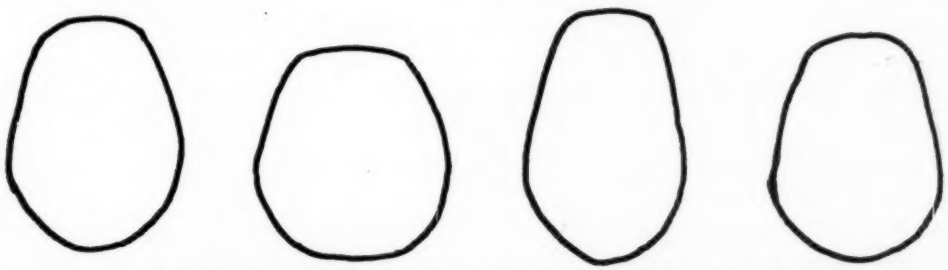
it, the blow on the underlying cortex is, as it were, " cushioned," and a wave of compression passes through the brain tissue toward the opposite side of the skull. When the compression wave reaches the cells of the cortex at the opposite side, these cells are suddenly thrown upon an unyielding surface, the skull, hence are damaged by the impact.

This theory is given as one way of describing the idea, perhaps most prevalent of all, that contre-coup injury is due to some form of " rebound " of the brain away from the part of the skull which is struck to the opposite side. It has the objection that the traumatic force should be greater at the point of application of the blow than at any other part, either coincidently or subsequently.

A 2. We might next postulate, by way of modification, an " elastic body " theory: Recently it has been shown by high-speed photography that when elastic bodies of various types, from golf balls and footballs to balls of steel, are struck they are deformed. They are deformed not only at the point struck but as a whole, and pass through changes in shape somewhat as is diagramatically represented in Fig. 7. It might be reasonable to suppose that the



A 1. "Compression Wave" or "Rebound" theory—deformation of skull at point of impact.



A 2. Elastic body theory—changes in shape of skull as a whole.

Fig. 7.—Diagrams to illustrate possible types of deformity of the skull at the moment of the blow.

skull should so behave, and that the sudden changes in position of the opposite side of the skull, perhaps meeting a compression wave transmitted through the brain tissue at different velocity and in an " out of phase " manner, might well produce injury at the opposite pole. Against this theory are, I believe, the composite anatomical structure of the skull, with its sutures and buttresses, and the fact that contre-coup will occur when fracture is present, for fracture of the skull theoretically should prevent these elastic changes in shape. The presence or absence of contre-coup in children and adolescents in whom the skull sutures are yielding might well be worth investigation from this point of view.

In its support we have the consideration that if such elastic vibrations occur they will tend to be most marked in amplitude on the unsupported side, i.e. in the region of contre-coup, much as if a bar of an elastic metal is made to strike the floor on one end, the end against the floor will be maintained more or less stationary while the free end may vibrate freely.

B. Do Differences in the Specific Gravity of the Intracranial contents play a significant rôle in Contre-coup Injury?

W. Ritchie Russell (1932) has advanced an explanation of the production of contre-coup on this basis. He makes several preliminary statements bearing on the problem:

1. That the brain fits the skull accurately, and that this, in addition to allowing the skull to bear the brunt of the blow, allows the strain exerted by the traumatic force to be distributed to all parts of the intracranial contents.

2. That the brain substance has greater specific gravity than the cerebrospinal fluid or blood, and will, therefore, tend to displace the latter.

3. That there is present within the skull a subarachnoid space containing cerebrospinal fluid which is capable of enlargement by reason of that fluid.

4. That the skull must not be considered as a closed box, for the jugular veins and foramen magnum can allow exit of blood, cerebrospinal fluid, and brain itself from the interior of the skull.

5. That the brain, for the above reasons, is capable of limited movement within the skull.

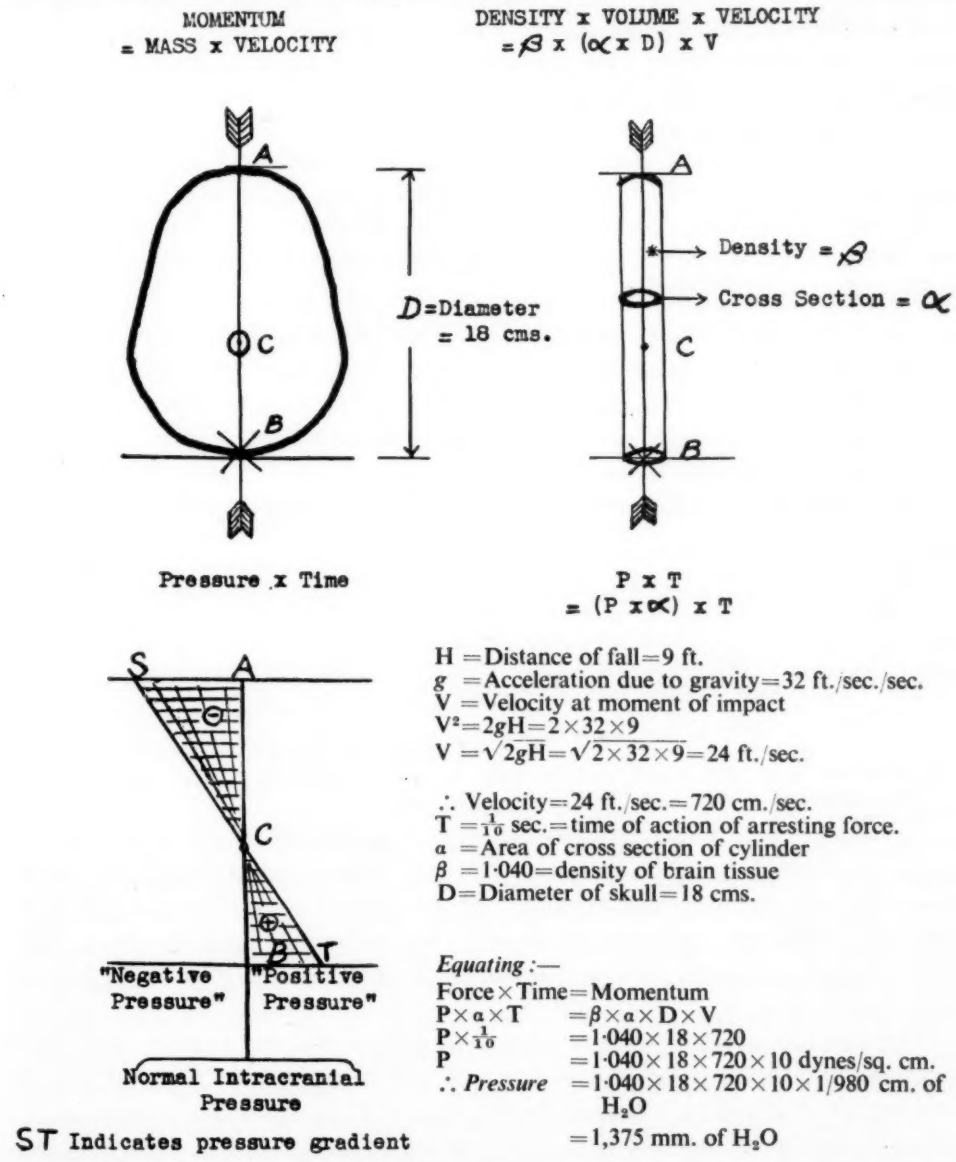
Ritchie Russell's explanation is roughly this: When the motion of the skull is suddenly arrested the brain, by reason of its momentum, carries on in the original direction by displacing the cerebrospinal fluid between it and the arrested skull and by forcing venous blood out of the skull. This motion of the brain relative to the skull is obviously greatest at a point diagonally opposite the point of contact. Since the subdural space cannot open up to allow this motion, whereas the subarachnoid space can do so by virtue of inflow of cerebrospinal fluid, there occurs a tearing-away of the brain from its trabecular attachments to the arachnoid membrane, which results in rupture of the small blood vessels running in the subarachnoid space and pia mater and entering the cortical substance. Thus, Ritchie Russell considers that in contre-coup injury the primary occurrence is a subarachnoid hæmorrhage and that the blood liberated from the torn vessels secondarily extends into the brain substance from its surface, causing destruction of cortical tissue.

Ritchie Russell's explanation is in many ways an attractive one, but it has several serious objections. First, there is the fact that in our observations (and, I believe, in that of Rand and Courville), the primary hæmorrhage in contre-coup injury is not subarachnoid but rather intracortical in position (Fig. 6). Observation of an area of mild contre-coup injury in the gross may not show any subarachnoid hæmorrhage. Secondly, the differences in specific gravity are so small and the time of action of the arresting force so short that it is highly unlikely that such displacement of cerebrospinal fluid as suggested

could occur. Thirdly, because fluids are relatively incompressible, unless the actual volume of the cranial cavity is changed no fluid could leave the skull under such an impact unless something of equal volume entered the skull coincidently.

C. The "Pressure Gradient" Theory

This theory differs from the others in that it deals entirely with pressure changes which occur within the skull whenever the moving skull is suddenly arrested in its motion or whenever the skull receives a heavy blow. It attempts to treat contre-coup as a problem in hydrodynamics, which may be simplified as follows (*see accompanying diagram, Fig.* 8).



H = Distance of fall = 9 ft.
g = Acceleration due to gravity = 32 ft./sec./sec.
V = Velocity at moment of impact
$V^2 = 2gH = 2 \times 32 \times 9$
$V = \sqrt{2gH} = \sqrt{2 \times 32 \times 9} = 24$ ft./sec.

$\therefore$ Velocity = 24 ft./sec. = 720 cm./sec.
$T = \frac{1}{10}$ sec. = time of action of arresting force.
α = Area of cross section of cylinder
β = 1·040 = density of brain tissue
D = Diameter of skull = 18 cms.

Equating :—

Force × Time	= Momentum
$P \times \alpha \times T$	$= \beta \times \alpha \times D \times V$
$P \times \frac{1}{10}$	$= 1{\cdot}040 \times 18 \times 720$
P	$= 1{\cdot}040 \times 18 \times 720 \times 10$ dynes/sq. cm.
$\therefore$ *Pressure*	$= 1{\cdot}040 \times 18 \times 720 \times 10 \times 1/980$ cm. of H_2O
	= 1,375 mm. of H_2O

Fig. 8.—Diagram illustrating the principles involved in the "pressure gradient" theory of the author.

Let us consider the skull as an incompressible shell, AB, filled with semi-fluid brain tissue with a communication to the exterior (the foramen magnum and jugular foramina) at C. Let us suppose it falls freely from a height H and is arrested by a resistant object in time T. Then, velocity at time of impact, $V=\sqrt{2gH}$, where g is acceleration due to gravity and H is distance of fall. This falling object has momentum by virtue of its weight and velocity.

Again, for simplicity, we need not consider the whole object but merely a cylindrical core of cross-sectional area α extending between A and B. The momentum of this cylinder will be equal to its mass $\times$ its velocity, i.e. its density $\times$ its volume $\times$ its velocity. At the instant of impact this momentum is counteracted by an arresting force acting on the cylinder between A and B, which we may measure as a pressure P per sq. cm. acting over a cross-sectional area α. This force, $P\times\alpha$, acts for a time T, which it requires to nullify the momentum of the falling cylinder.

We may equate these:

arresting force $\times$ time = momentum of cylinder,
or $P\times\alpha\times T$ = density $\times$ volume $\times$ velocity of cylinder.
Let us now substitute estimated values for these symbols as follows:
Let H = distance of fall = 9 ft.

g = acceleration due to gravity = 32 ft./sec./sec. = 980 cm./sec./sec.
V = velocity at moment of impact = $\sqrt{2gH}$ = 24 ft./sec. or 720 cm./sec.
T = time of action of arresting force = $\frac{1}{10}$ sec.
α = cross-sectional area of hypothetical cylinder.
β = density of brain tissue = 1·040 grams.
D = diameter of skull = distance between A and B = 18 cm.

Then, continuing our equation:

$$P\times\alpha\times T=\text{density}\times\text{volume}\times\text{velocity of cylinder}=\beta\times(\alpha\times D)\times V.$$

$$P\times T=\beta\times D\times V$$

$$P\times\tfrac{1}{10}=1{\cdot}040\times 18\times 720$$

$$P=1{\cdot}040\times 18\times 720\times 10 \text{ dynes/sq. cm.}$$

$$=\frac{1{\cdot}040\times 18\times 720\times 10 \text{ cm.}}{980} \text{ of water} = 137{\cdot}5 \text{ cm. of water.}$$

Pressure = P = 137·5 cm. H_2O = 10·1 cm. Hg.
= 1375 mm. H_2O = 101 mms. Hg., approx.

As we have intimated, this pressure P is distributed through the brain tissue (of the hypothetical cylinder) in the nature of a pressure gradient with the maximum pressure at B and the minimum pressure at A, for every particle contained in the cylinder must be acted upon by the arresting force.

The absolute pressure at any point will depend on the position of C, the communication with external pressure. If this is midway between A and B the pressure at B will be increased by 675 mm. of H_2O, while the pressure at A is diminished by 675 mm. of H_2O. If C is nearer to B than it is to A then the pressure at B is increased by less than this amount and the pressure at A

diminished by more than this amount. Thus, in the common occipito-frontal type of contre-coup, if AC=2×CB, then pressure at A would be diminished by *920 mm. H_2O*, while pressure at B is increased by 460 mm. H_2O pressure. (See diagram of pressure gradient, Fig. 8.)

Thus, if we accept the simplifying assumption made, we may conclude that when a man's head falls 9 ft. under the action of gravity and is arrested in one-tenth of a second, or when it falls a lesser distance and " bounces," or when a man's head travelling at 16 miles per hour is arrested in one-tenth of a second, a pressure gradient is set up momentarily with the skull of the order of magnitude of 1,375 mm. of water with a maximum *fall of pressure* at the point of brain surface diametrically opposite to the point of application of the force, that is, in the area of contre-coup of 675 mm. of water or more (50 mm. mercury or more). It is to be noted that this pressure fall will be greatest in the occipito-frontal type of trauma which we have shown has by far the highest incidence of contre-coup.

The severity of the pressure gradient will be modified in the actual case by the possibility of actual skull deformity and by the fact that the foramen magnum and jugular foramina do not communicate directly with the outside air (but venous sinuses are at atmospheric pressure).

Here, then, is a dramatic intracranial event occurring at the moment of impact of a traumatic force to the head. Is it the cause of contre-coup hæmorrhage? Fortunately for the individual these changes in pressure will tend to occur in all the intracranial contents coincidently, and will, therefore, involve the blood in the blood vessels coincidently with the surrounding tissues. But, on the other hand, these blood vessels contain a fluid which is circulating and which is constantly under the pressure of a force pump which is itself not influenced at all by these changes inside the skull. It is, therefore, conceivable that a pressure imbalance is momentarily set up and that the small blood vessels in the area of contre-coup are distended and ruptured by a sudden release of external pressure which is not completely met by a fall in intravascular pressure due to circulatory inflow from an outside pressure source, the contraction of the left ventricle of the heart.

D. Do Rotation Effects play a part in the production of Contre-coup Injury?

We have observed that the fronto-temporal region is the area of predilection for the occurrence of contre-coup. Here the irregular structure of the skull, particularly the orbital surface of the frontal bones and lesser wings of the sphenoids, contrast strongly with the smooth shelving surface in other parts. Damage here certainly seems to suggest movement of brain against the skull. There is a type of movement seldom mentioned, which may often occur, namely rotation. When a head is struck by a blow or a fall it is seldom struck squarely and a rotatory component is often present. Anyone who has rotated a glass of water and seen the water stand still while the glass rotates, will realize that such a phenomenon in operation in the skull might well cause damage to the brain in a region where body projections are present.

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HEAD INJURIES AND MENINGITIS

BY

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(RECEIVED 11TH NOVEMBER, 1940)

Introduction

THE following cases have been selected from the files of the Division of Neuropathology in the University of Toronto to illustrate the types of head injury which may cause death from meningitis. The fatal infection of the meninges may occur at the time of the injury, killing the patient within a few days or weeks of the accident, but its onset may be delayed for years after the head injury. Three of the seven cases described below fall into the latter group, the patients having apparently recovered from their head injuries shortly after their accidents and having shown no symptoms until the sudden onset of a rapidly fatal meningitis.

The pneumococcus was the organism responsible for the meningitis in all these cases and, except for some variations mentioned in the text, the gross and microscopical pathological picture was typical of pneumococcal meningitis.

Case Reports

Case 1: M. W. (NP: 315–34), a man of 30 years, was probably kicked in the face by a horse on the 22nd October, 1934, although he could remember no details of the accident. He remained conscious but vomited several times during the next two days. He became unconscious on the 24th October and rapidly developed the signs of meningitis of which he died on the 26th October, four days after his accident.

Post mortem.—There was severe laceration of the face, with fractured nasal bones. Removal of the brain showed severe hæmorrhage covering the floor of the anterior cranial fossæ. The bone of these fossæ was shattered around the crista galli, which was loose, freely movable and displaced to the left. Scissors could be passed easily from the cranial cavity into the nasal fossæ. A fracture 3 cm. long radiated outwards into the left orbital plate of the frontal bone.

There was greenish-yellow purulent exudate in the subarachnoid space. Pneumococci were cultured from this exudate and from the cerebrospinal fluid.

Comment.—This, then, is a case of rapidly fatal meningitis following an injury to the face of which the main external sign was simple fracture of the nasal bones.

Case 2: L. W. (NP: 170–36), a man of 50, was riding a bicycle when he was hit by a truck on the 21st May, 1936. On admission to hospital he was conscious but irritable. There was considerable bleeding from the back of the nose, with hæmatemesis. Leakage of cerebrospinal fluid from his nose was noted on 25th May. On the following day spinal puncture withdrew turbid fluid containing large numbers

of polymorphonuclear leucocytes. His temperature rose till his death on the 27th May, six days after the accident.

Post mortem.—There was a large area of subcutaneous hæmorrhage on the left side of the scalp extending into the temporal muscle. Extradural hæmorrhages were found in the left anterior and middle cranial fossæ. A complicated fracture of the base of the skull began at the outer end of the left supra-orbital ridge. This extended backwards and inwards, crossing the midline through the body of the sphenoid bone and running along the antero-inferior border of the petrous portion of the right temporal bone to end in the right middle-ear cavity which was full of blood. A branch of this fracture extended inwards completely encircling the cribriform plate of the ethmoid and from here ran into the right frontal sinus which was pneumatizing the right orbital plate of the frontal bone. A second branch of the main fracture extended backwards and outwards across the left middle cranial fossæ to end in the base of the petrous portion of the left temporal bone. The sphenoidal and ethmoidal sinuses contained purulent exudate mixed with hæmorrhage.

Culture taken from the base of the brain yielded pneumococcus type 4 and there was well-marked purulent exudate in the subarachnoid space.

Comment.—This case is reported because it illustrates a basal skull fracture which had opened practically all the accessory nasal sinuses as well as both middle ear cavities. Purulent exudate in the frontal and ethmoidal sinuses was responsible for the meningitis in this case.

Case 3: R. T. (NP: 371–39), a boy of 3 years, was hit by a motor car shortly before his admission to hospital on the 17th September, 1939. Four days later he developed pneumococcal meningitis for which he received antipneumococcal serum combined with sulphapyridine. He gradually went down hill with persistence of his symptoms till his death on the 15th October, about a month after the trauma. There was no clinical evidence of fracture of the skull.

Post mortem.—There was an area of extradural hæmorrhage in the right posterior cranial fossæ. This overlay a fracture which began slightly below and to the right of the external occipital protuberance. The fracture ran downwards and outwards to reach the petrous portion of the right temporal bone. It then ran inwards to end in the apex of this bone. Both middle-ear cavities showed evidence of chronic inflammation. There was also a mottled grey and dark-red thrombus in the lumen of the right lateral sinus in relation to the line of fracture. There was massive purulent exudate in the basal subarachnoid space.

Comment.—This case is of interest because the relationship of the head-injury to the meningitis was obscure until it was revealed at post mortem. It also illustrates the danger of chronic middle-ear disease in cases of fracture of the base of the skull. Finally the life of the patient was prolonged for nearly a month after the onset of meningitis, probably by the serum and sulphapyridine therapy.

Case 4: J. B. (NP: 164–37), a man of 49 years, was unconscious for 20 minutes following a fall downstairs on to a cement floor in the evening of the 12th February, 1937. On his recovery of consciousness he complained of severe frontal headache and he vomited. On admission to hospital the following day there was tenderness and œdema over the left parieto-occipital region of the scalp. His right knee-jerk was brisk and there was a doubtfully positive right Babinski. His cerebrospinal fluid pressure was high. There was no X-ray evidence of fracture of the skull.

Two days later, on the 15th February, he began to develop evidence of left otitis media, which required paracentesis of the drum on the 1st March. By the 11th March he showed a complete right hemiplegia with aphasia. On the following day an opera-

tive exploration revealed an infected left subdural hæmatoma from the contents of which pneumococcus, Type 3, was isolated. He improved temporarily but the development of a cerebral hernia obstructed efficient drainage of the infected subdural space and he gradually became more comatose, dying on the 24th April, $2\frac{1}{2}$ months after his accident.

Post mortem.—A linear fracture, 10 cm. long, ran horizontally through the lateral portion of the base of the occipital bone on the left side into the petrous portion of the left temporal bone. This bone was softened and contained purulent material.

The brain showed the infected left subdural hæmatoma, which had been opened and partially drained by operation. A horizontal section through this man's cerebral hemispheres is shown in Fig. 1.

Fig. 1.—Photograph of a horizontal section of the cerebral hemispheres of Case 4, showing the area of herniation of the left cerebral hemisphere. The undrained portion of the old infected subdural hæmatoma is seen lying over the left frontal lobe. There are two small subcortical abscesses in the herniated tissue of the left fronto-parietal area.

Comment.—This is a case in which infection from the patient's left middle-ear cavity and petrous temporal bone had been able to spread upwards through an unsuspected fracture line to infect a traumatic subdural hæmatoma, causing his death two and a half months after his fall.

Case 5: D. B. (NP: 176–39), was a professional jockey 22 years of age when he died on the 16th May, 1939. In 1934 he had had his nose broken by a horse. The skin laceration required sutures and he was in hospital for 11 days at that time. There were no significant after-effects.

On the 12th May, 1939, 5 years later, he had a slight cold in the head. Two days later he had a headache in the morning, by 3 p.m. he was vomiting and having convulsions. He was admitted to hospital comatose at 6 p.m. with all the signs of meningitis. The right maxillary and frontal sinuses were opaque to transillumination. Pneumococci were seen in a smear of his cerebrospinal fluid. In spite of vigorous treatment by soludagenan he died on the 16th May, four days after his first complaint of cold in the head.

Post mortem.—The left olfactory bulb and the adjacent frontal lobe were adherent to the cribriform plate of the ethmoid over the anterior ethmoidal air cells. The dura mater covering this area was hyperæmic and its inner surface had lost its lustre due to adhesion to the overlying leptomeninges and brain. The crista galli was deviated to

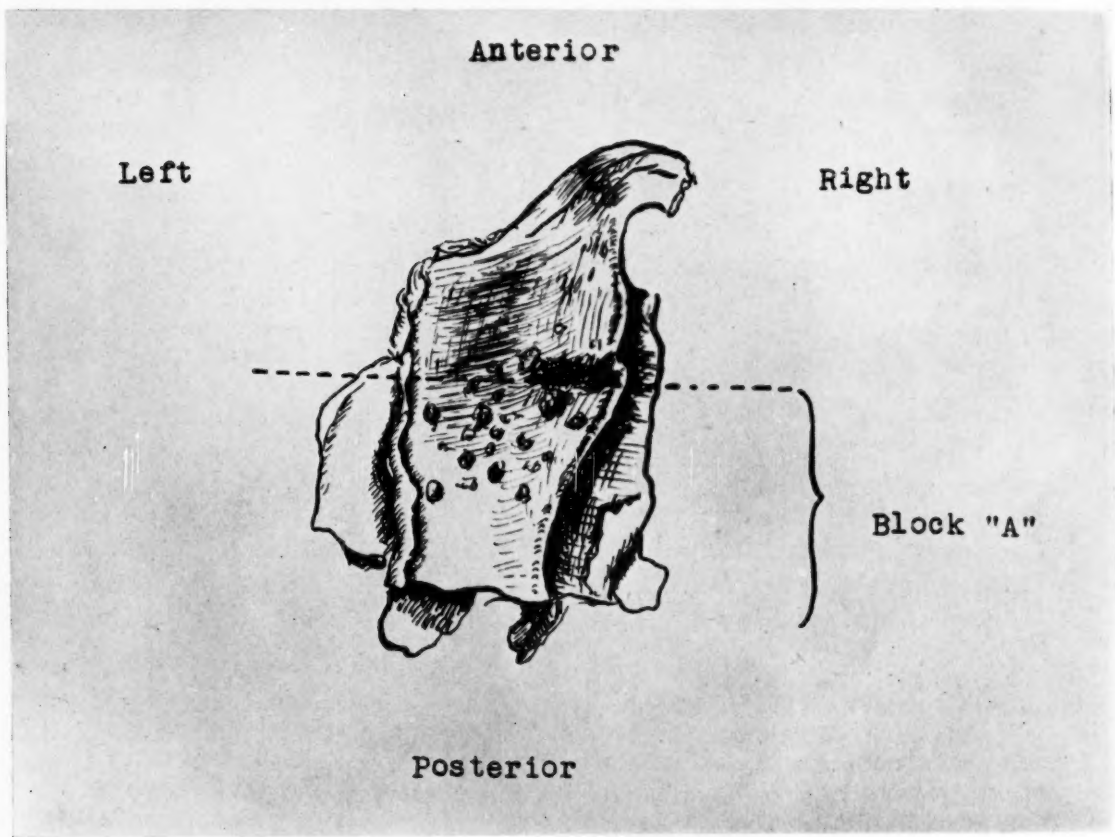

Fig. 2.—Sketch of the upper surface of the cribriform plate of the ethmoid of Case 5. The crista galli is markedly deviated to the right. Scattered tags of friable tissue, yellowish with old blood-pigment, were attached to the left side of the crista galli, representing the area of dense adhesion to the overlying meninges and frontal lobes. The dotted line shows the plane of the vertical section through the bone shown in Fig. 3.

the right (Fig. 2), and there was old blood pigment covering the left side of the cribriform plate. There was pus in the right and left ethmoidal sinuses. Microscopical examination of a vertical section cut through the area of old trauma to the cribriform plate of the ethmoid in the plane of the dotted line shown in Fig. 2 is shown in Fig. 3. This demonstrates, under low magnification, the pathway of the patient's acute terminal pneumococcal infection from the roof of the right nasal fossæ to the overlying adherent leptomeninges.

There was no gross purulent exudate in the subarachnoid space, but widespread meningitis was seen microscopically.

Fig. 3.—A low-power photomicrograph (×14) of a vertical section through the cribriform plate of the ethmoid of Case 5. This shows the roof of the right nasal fossæ, to the left of the photograph, with the nasal septum between the two nasal cavities. It demonstrates the pathway of infection from the right nasal fossæ to the overlying, adherent leptomeninges.

Comment.—An illustration of an important type of case, further illustrated by Case 6, in which an apparently trivial facial injury did sufficient damage to the cribriform plate of the ethmoid to provide a pathway for the passage of a pneumococcal nasal infection to the adjacent leptomeninges, causing death from a fulminating meningitis, five years after the original injury.

Case 6: W. P. (NP: 198–37), a man of 36 years at the time of his death, had an injury 14 years before, when he was hit in the midline of the forehead by the limb of a falling tree. He was unconscious for some hours and was off work for about two months. After this time he had complained of intermittent headaches often sufficiently severe to prevent his working.

In 1931 an X-ray showed a fracture near the midline of the vertical plate of the frontal bone extending obliquely downwards and outwards through the left frontal sinus and into the left ethmoidal cells. Late in May, 1937, he went to his doctor complaining of a foul-smelling nasal discharge. Increasing severity of headache necessitated his stopping work on the 4th June. He became confused and drowsy

by the 6th June and was admitted to hospital in extremis on the following day. His cerebrospinal fluid on his admission was found to be opalescent and under greatly increased pressure. He died 17 hours later.

Post mortem.—The gross pathological findings were very similar to those recorded in Case 5. The orbital surface of the left frontal lobe was densely adherent in the region of the cribriform plate. An old fracture of the anterior cranial fossæ was found under this adherent area. It extended from the left optic foramen forwards and inwards to the cribriform plate and then turned backwards towards the right optic foramen. This fracture of the anterior cranial fossæ was considered to be a continuation of the frontal bone fracture seen by X-ray examination in 1931.

Seromucoid discharge was found in the sphenoidal and ethmoidal air sinuses. There was bronchopneumonia in the lower lobes of both lungs. Pneumococcus, Type 4, was cultured from the blood and from the cerebrospinal fluid. A vertical section cut to include the lines of old fracture of the cribriform plate of the ethmoid and of the right supra-orbital plate has been photographed under low magnification (Fig. 4). This shows an old fracture healed by fibrous tissue in the roof of the right

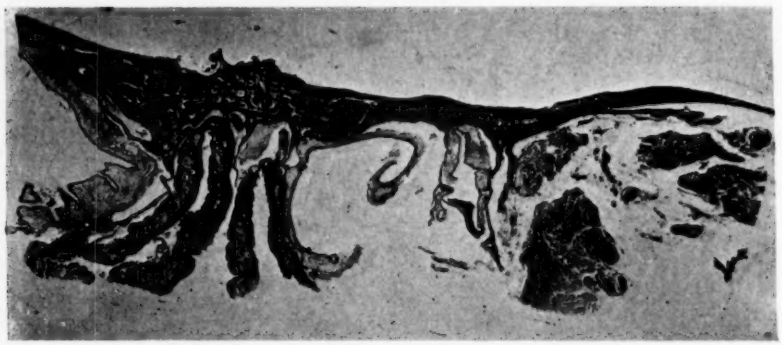

Fig. 4.—A low-power photomicrograph of the anterior cranial fossæ and adjacent structures of Case 6. This shows, from right to left, the right orbit, the right ethmoidal sinus, the nasal fossæ and the left ethmoidal sinus. In the plate of bone covering the right orbit an old fracture line can be seen extending through the thickness of the bone. Over the nasal fossæ another portion of the line of old fracture is shown by proliferated cancellous bone, with wide channels running through it.

orbit. This is shown under high magnification in Fig. 5. The second line of fracture, in the region of the cribriform plate, shows considerable proliferation of cancellous bone. This is shown under higher magnification in Fig. 6. Many of these cancellous spaces, especially those in relation with the infected left ethmoidal sinus, seen to the left of the photograph, contains large numbers of inflammatory cells (Fig. 7).

Comment.—In this case, therefore, it was concluded that the patient's terminal pneumococcal infection had spread from his acutely infected ethmoidal and sphenoidal sinuses through the site of a fourteen-year-old fracture in the cribriform plate of his ethmoid to the overlying, adherent leptomeninges, accounting for the meningitis of which he died. This viewpoint of the case was accepted by the Workmen's Compensation Board of Ontario and the widow was granted a pension for her husband's head injury.

Case 7: P. H. (NP: 31–34), a man of 52 years, died of a fulminating pneumococcal meningitis on the 15th January, 1934. On the 27th September, 1931, he had shot himself accidentally with a ·22 rifle. The bullet entered below the chin and passed upwards through the soft-palate just to the left of the midline. He did not lose consciousness. There were no positive neurological findings and no leakage of cerebro-

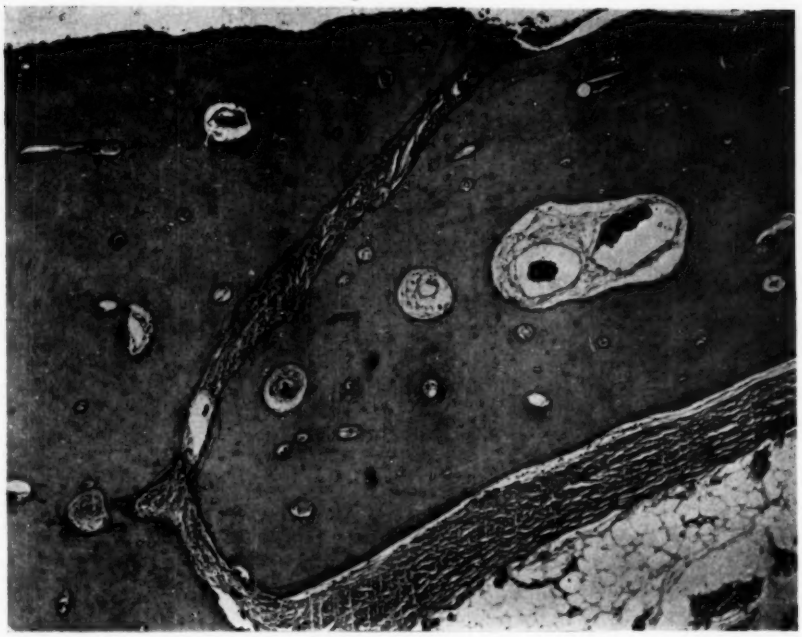

Fig. 5.—Higher magnification of the fracture line in the roof of the orbit in Case 6. This shows union of the fractured surfaces by fibrous tissue. The periosteum of the roof of the right orbit and orbital fat are shown in the lower part of the photograph.

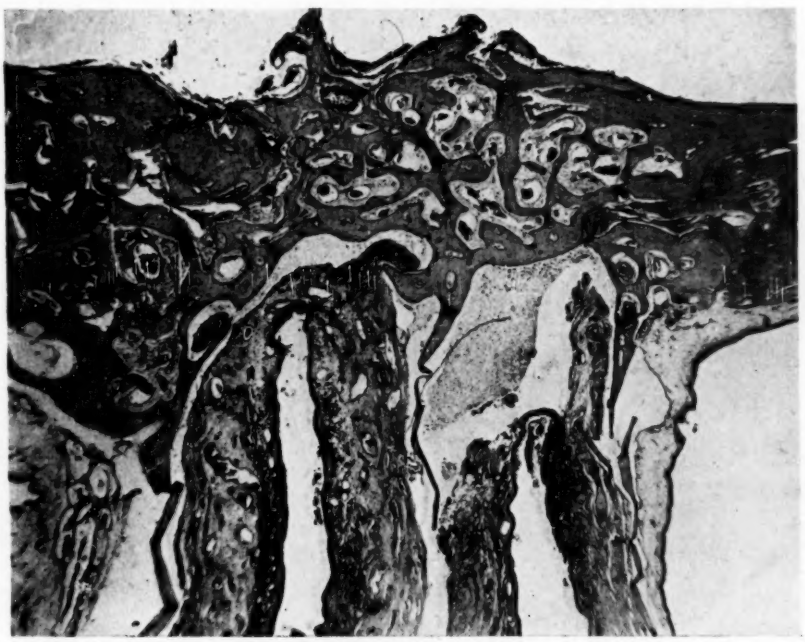

Fig. 6.—Proliferated cancellous bone at the site of the old fracture above the nasal fossæ of Case 6. Under this higher magnification inflamed and œdematous mucous membrane of the left ethmoidal sinus is seen to the extreme left of the photograph. The cancellous spaces in the bone overlying this sinus contain an acute inflammatory cellular reaction mixed with fibrous tissue (see Fig. 7).

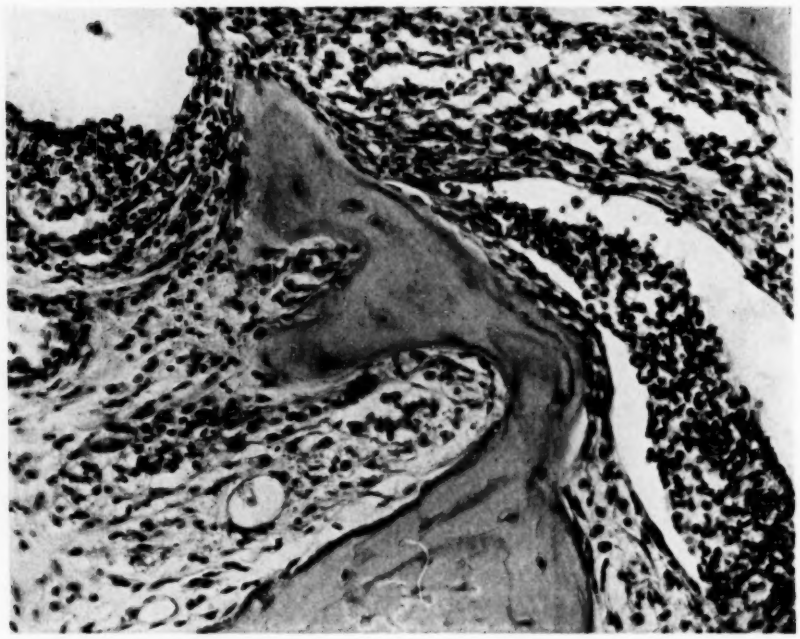

Fig. 7.—A higher power photomicrograph of the cancellous bone seen in Fig. 6, showing detail of the acute inflammatory reaction in the cancellous spaces at the site of a fourteen-year-old fracture. The terminal infection is believed to have reached the meninges from the acutely inflamed sinuses by this route.

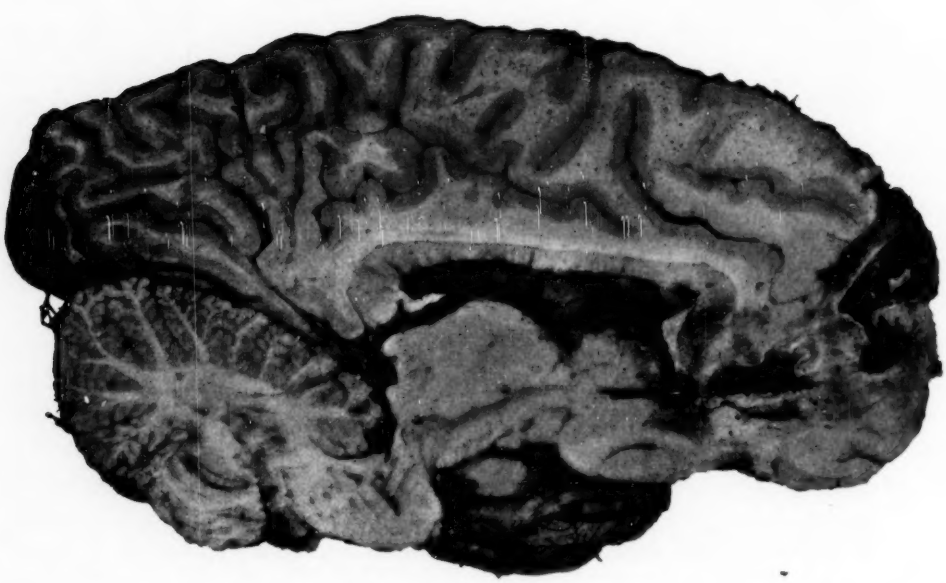

Fig. 8.—A para-sagittal section of the left cerebral hemisphere of Case 7, showing two pneumococcal abscesses in the line of the 2½-year-old bullet track. The lower abscess has ruptured into the anterior horn of the left lateral ventricle causing the patient's terminal ventricular and meningeal infection.

spinal fluid. The bullet was seen by X-ray to be lying inside the vertex of the skull over the left frontal lobe just to the left of the superior sagittal sinus. On the following day the bullet was easily removed through a small left frontal bone-flap. The bullet track was explored with a soft rubber catheter which was passed from above through the left frontal lobe and through the bullet entry wound. After the operation the lower end of the catheter was seen by X-ray to be lying on the upper surface of the soft palate. It was gradually removed from below and the patient made an uninterrupted recovery.

He continued to work steadily and with no disability until a few days before his death, $2\frac{1}{2}$ years later, when he developed a slight cold followed by a fulminating pneumococcal meningitis.

Post mortem.—The old bullet entry wound in the posterior part of the left orbital plate was covered by fibrous tissue. Its margin was continuous with a posterior ethmoidal air-cell. The bullet had passed upwards between the left optic nerve laterally and the left anterior cerebral artery mesially. The exit wound of the bullet from the brain was seen at the supero-mesial border of the left frontal lobe, 2·5 cm. behind its pole. A para-sagittal section cut to the left of the midline in the line of the bullet track (Fig. 8), shows two abscesses in the left frontal lobe in the line of the bullet track. The lower abscess has broken into the cavity of the left lateral ventricle to produce the patient's terminal ventricular and meningeal infection.

Comment.—This case is of interest in suggesting that pneumococci had probably remained alive in the bullet-track for a period of two and a half years, during which time they gradually produced two asymptomatic brain abscesses in the patient's left frontal lobe. It is also intriguing to wonder whether the cause of the rupture of the abscess into the ventricle was the sudden increases of intracranial pressure, which probably occurred when he coughed and sneezed with his cold in the head. In this case there was no suggestion of a recent invasion of the cranial cavity by pneumococci from the nasal fossæ.

Summary

(1) Seven cases of meningitis are described in which the fatal infection followed a fracture of the base of the skull.

(2) In three of these cases the meningitis occurred 14, 5 and $2\frac{1}{2}$ years, respectively, after injury.

THE EFFECT OF CHOLIN-LIKE SUBSTANCES ON THE CEREBRAL ELECTRICAL DISCHARGES IN EPILEPSY

BY

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(RECEIVED 11TH MARCH, 1941)

IN a recent paper (Williams and Russell, 1941) the effects of anticholinesterases on petit mal epilepsy were described. Clinical and subclinical attacks were recorded on the electro-encephalogram (e.e.g.) in epileptic subjects who were selected either for the frequency of their spontaneous attacks, or for the ease with which attacks could be induced. A dose of eserine insufficiently large to cause symptoms through its effect on the parasympathetic system in man was found to prevent petit mal activity, whereas a larger dose caused an increase in the number and duration of petit mal attacks. Prostigmin on the other hand invariably caused an increase in the epileptic activity seen in the e.e.g. and it reversed the effect of small doses of eserine. The work has been continued in an attempt to establish the mode of action of these drugs and to discover the effect of other substances known to modify transmission at cholinergic endings. The present paper contains observations on the effect of acetylcholine and allied drugs upon the incidence of epileptic cerebral discharges, and the results are discussed in relation to the site of action of the substances.

Methods

As the experimental procedure did not differ greatly from that already described (Williams and Russell, 1941) it will only be referred to briefly. Epileptic patients and normal subjects were used. They sat or lay comfortably at rest with the eyes closed while an e.e.g. record was obtained from two solder electrodes sealed to the scalp over the frontal and parietal lobes with collodium simplex, contact being made with Cambridge electrode jelly. The electrodes led to a condenser coupled amplifying system which was connected to a Grass ink writing oscillograph. This recorded the difference in electrical potential between two widely separated areas of the cortex, and as the cerebral electrical changes associated with clinical fits involve the whole cortex and those seen in subclinical attacks are usually propagated over a wide area, this method of recording proved adequate for the investigation, which only dealt with the number and duration of attacks. Time was recorded in seconds and minutes and in some cases electrocardiographic and respiratory tracings were made simultaneously with the e.e.g. The experimental procedure and clinical signs and symptoms were noted on the moving record as they occurred.

The periodicity of spontaneous epileptic attacks is usually too variable for their incidence to be used as a quantitative index in an experimental method lasting for a few hours only; therefore a standard procedure which would induce attacks at fixed intervals under controlled conditions was used in some cases to provide a measurable criterion of the anticonvulsive effect of the substances under examination.

The most simple and effective method of inducing petit mal is by overbreathing, which eliminates CO_2 and temporarily raises the blood *p*H (Gibbs, Lennox and Gibbs, 1940). Petit mal outbursts usually occur with the readjustment of the acid base balance after hyperventilation has ceased (Nims *et al*, 1940). Subjects were therefore instructed to overbreathe for a period of 100 seconds every 10 to 20 minutes during the experiment and to maintain the same depth of overbreathing each time. The expired air was collected in a Douglas bag and measured. Repeated records were taken before and after injection of the drugs under similar experimental conditions and the same subject was used to investigate several drugs. A record of a typical series of epileptic discharges after overbreathing has already been published (Williams and Russell, 1941). The duration of these discharges, measured during and after each period of hyperventilation, was taken to represent the total epileptic activity resulting from the preceding hyperventilation, the factor being plotted graphically after each experiment (see Fig. 3).

By selection from a large number of patients, six subjects were found who had very frequent spontaneous epileptic attacks. In these cases the incidence of the spontaneous subclinical attacks was so regular and their number so great that their occurrence in consecutive e.e.g. records could be compared. In these subjects no attempt was made to induce attacks but they merely sat or lay quietly while repeated e.e.g.'s were taken at fixed intervals before and after administration of drugs.

Eserine, prostigmin, pilocarpine, carbaminoylcholine chloride, and atropin sulphate were injected subcutaneously, while acetylcholine alone and with atropin was given intravenously.

In describing the results, the terms epileptic " outbursts " or " attacks " refer to the characteristic discharges seen in the e.e.g. whether or not clinical evidences of the attack were present. This broad conception of epilepsy simplifies the description considerably.

Results

Eserine and Prostigmin.—The observations previously reported (Williams and Russell, 1941) have been made in two further subjects who had frequent spontaneous epileptic attacks, and similar results were obtained.

One subject (G.G.C.), aged 16½, had had attacks since he was 8 months old. Until the age of 8 he had momentary lapses of consciousness when his head fell forwards for a moment and he dropped articles he was holding. He did not fall to the ground. When 12 years of age he began to have nocturnal grand mal attacks every 10 days or so. When seen he was having two to six attacks a day which he described as " losing touch for a moment with what is going on," with a grand mal attack in his sleep about once a fortnight. There was no family history of epilepsy, and the patient was physically and mentally normal.

The e.e.g. showed an abnormal outburst characteristic of petit mal (Fig. 1) at short intervals. The patient was not aware of any subjective change when these outbursts took place, and no clinical attacks were observed during any experiments. A subcutaneous injection of eserine salicylate 1·0 mgm. caused a diminution in the number of outbursts, with complete cessation from 37 to 68

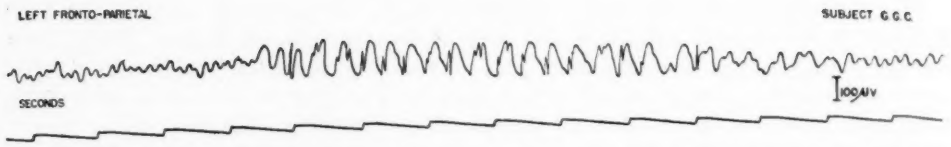

Fig. 1.—The tracing of an electro-encephalographic record taken during a subclinical petit mal attack in the subject G.G.C.

minutes after the injection (Fig. 2). The patient said he felt a little hot but had no other symptoms after the injection. A dose of 0·8 mgm. of prostigmin subcutaneously did not alter the incidence of the outbursts and had no subjective effect, but 1·25 mgm. caused an increase in the number of attacks 45 minutes after injection. The patient did not complain spontaneously of any symptoms but he was a little flushed and there was slight sweating.

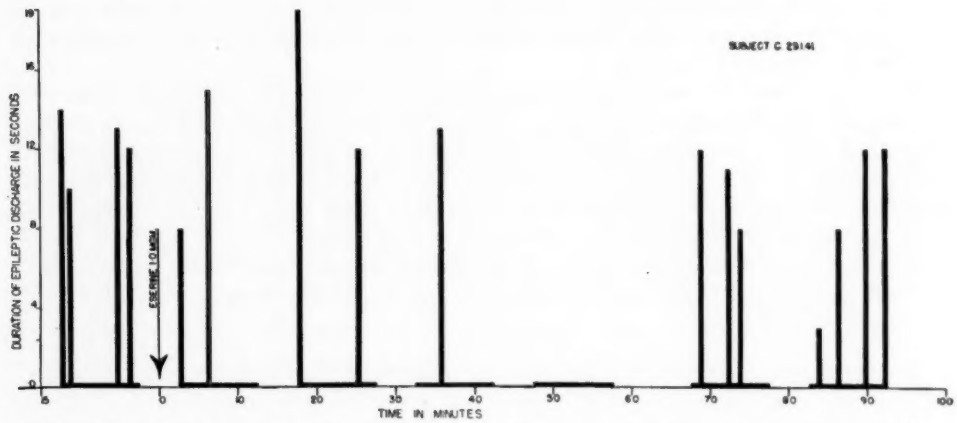

Fig. 2.—The effect of a subcutaneous injection of 1·0 mgm. Eserine on the number and duration of petit mal attacks, similar to that illustrated in Fig. 1, in subject G.G.C. Records were run for 10-minute periods, represented by the thick lines along the abscissa. Each vertical line represents one petit mal attack.

Carbaminoylcholine Chloride.—Chloryl (Savory and Moore) was injected subcutaneously in doses of 0·25 mgm. on eight occasions in three epileptic patients who showed petit mal discharges on the e.e.g. and four times in normal controls. In two of the epileptic subjects in whom subclinical attacks were induced by overbreathing in standard conditions there was an increase in the epileptic response to hyperventilation (Figs. 3 and 5). In two patients in whom spontaneous epileptic discharges could be recorded six experiments were performed. In three there was a great increase in the epileptic activity, in two there was a moderate increase, and in one no significant change was seen. An example of the results obtained is shown in Fig. 4. The effect of the drug appeared about 25 minutes after the injection was made. In subjects in whom the attacks were induced by overbreathing the effect lasted for about 30 minutes, but in those in whom spontaneous attacks only were recorded the effect was shorter.

Reference to Figs. 4 and 5 shows that in predisposed subjects epileptic cerebral discharges could be precipitated by the subcutaneous injection of

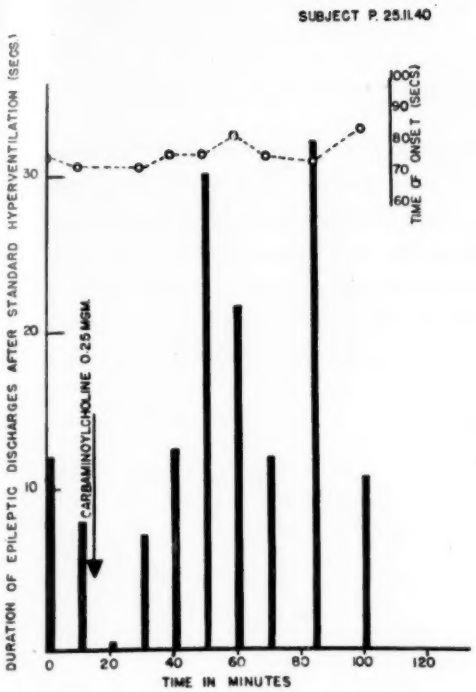
SUBJECT P. 25.11.40
DURATION OF EPILEPTIC DISCHARGES AFTER STANDARD HYPERVENTILATION (SECS.)
TIME OF ONSET (SECS.)
CARBAMINOYLCHOLINE 0·25 MGM.
TIME IN MINUTES

Fig. 3.—The effect of subcutaneous injection of 0·25 mgm. carbaminoylcholine chloride on petit mal activity induced by overbreathing in an epileptic subject. Each vertical line represents the length of time occupied by petit mal activity, seen in the e.e.g., after 100 seconds of overbreathing. The time of onset of the petit mal attack after beginning overbreathing is constant although the duration of petit mal is increased.

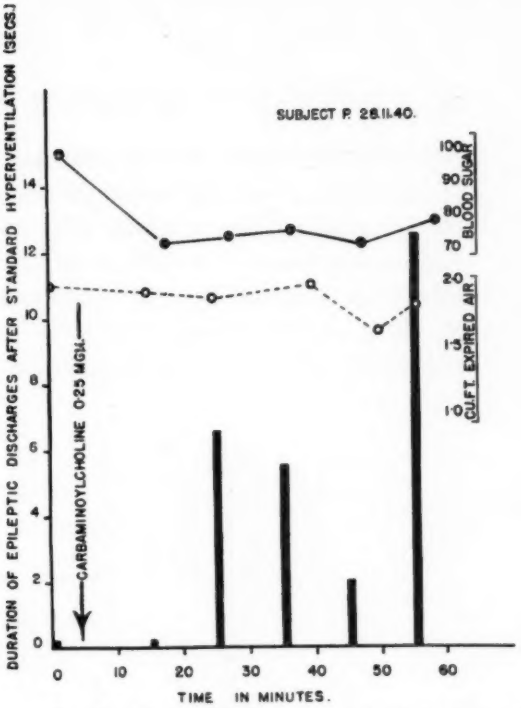

Fig. 5.—Twenty-five minutes after injection of 0·25 mgm. carbaminoylcholine chloride 100 seconds of overbreathing is followed by an outburst of petit mal, although previous overbreathing had not produced any epileptic activity under similar conditions. The graph has the same characteristics as that in Fig. 3. The volume breathed during each period of hyperventilation is fairly constant. Blood sugar is represented in mgm. per 100 c.c.

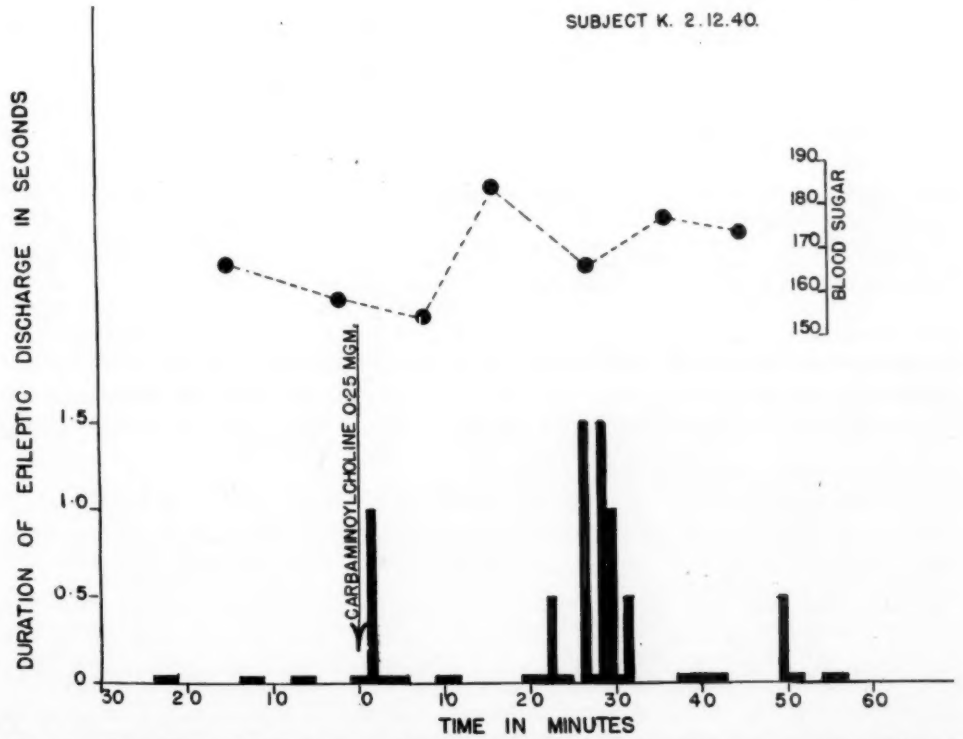

Fig. 4.—The effect of 0·25 mgm. carbaminoylcholine chloride upon spontaneous petit mal attacks, seen in the e.e.g., in subject K. The columns have the same significance as in Fig. 2. The record was obtained shortly after a meal and blood sugar is plotted in mgm. per 100 c.c. There is no significant change in the blood sugar level as a result of the injection.

carbaminoylcholine chloride although no epileptic activity was present at all during control periods before the injection was given. When records were continued for sufficiently long after the injection had been made—for a period of about an hour—the epileptic activity again disappeared (Fig. 4). Not only was the incidence of the discharges greater, but their duration was increased by the drug and the results showed that the action in spontaneous or artificially induced attacks was identical in this respect. The doses used were not sufficient

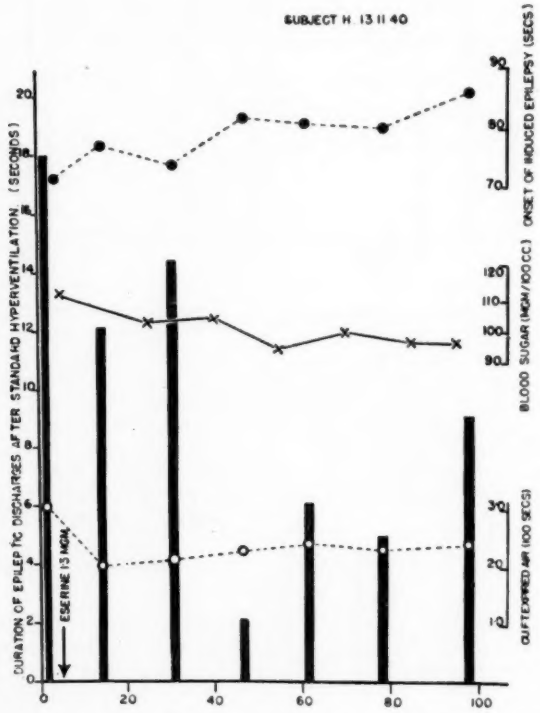

Fig. 6.—The effect of subcutaneous injection of 1·5 mgm. of Eserine on the amount of petit mal activity induced by 100 seconds of overbreathing. The columns have the same significance as in Fig. 3 and the abscissa represents time of experiment in minutes. The onset of attacks after beginning overbreathing, the volume breathed during each period of hyperventilation, and blood sugar in mgm. per 100 c.c. are plotted.

to cause any marked clinical effect and none of the subjects complained spontaneously of any discomfort. There was occasionally bradycardia, and the pulse rate fell from 68 to 54 in one subject. Some patients were a little flushed and there was occasional slight sweating.

When subcutaneous injection of atropin sulphate gr. 1/100 was made shortly before the injection of carbaminoylcholine chloride the effect of the second drug was either abolished or greatly diminished. Fig. 7 shows such an effect in a subject who had been given carbaminoylcholine chloride alone with striking effect the previous day. This patient (subject K) was used repeatedly in the examination of many of the substances investigated and a short clinical history is given later.

Petit mal activity is readily modified by alterations in the blood sugar level,

an increase preventing attacks and a decrease inducing them (Gibbs, Gibbs and Lennox, 1939). Changes in the blood sugar level have been reported after injection of cholin-like substances (Hrubetz, 1937), so that blood sugar estimations were made immediately after the e.e.g. records were taken, in case changes had occurred with the doses used in these experiments. Blood was obtained from a superficial vein of the forearm and determinations were made by the Folin Wu method. The results were plotted as in Figs. 5 and 6. There was

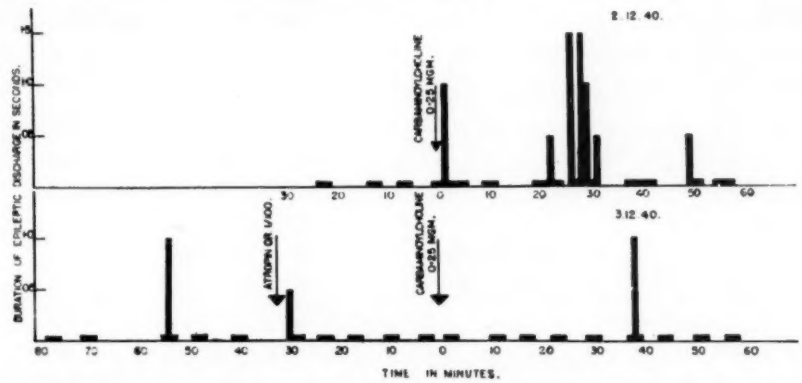

Fig. 7.—Inhibition of the effect of carbaminoylcholine chloride upon petit mal by atropin. As in Fig. 6 the thick lines along the abscissa represent periods of recording of the e.e.g. and the vertical lines each represent a petit mal attack.

no relationship between the small fluctuations in blood sugar level and the alteration in the amount of epileptic activity, nor was any constant change in blood sugar level seen after the injections had been made.

Acetylcholine.—Acetylcholine hydrochloride (B.D.H.) was injected intravenously on six occasions in two epileptic patients and six times in normal controls. Intelligent, co-operative subjects were chosen and symptoms of an intravenous injection of acetylcholine (Carmichael and Fraser, 1933) were described to them to allay apprehension. They lay with their eyes closed and a continuous record was made of the e.e.g. and electrocardiogram. After a control run the needle was introduced into a superficial vein of the forearm and a further control run was obtained. Care was taken to prevent entry of any blood into the syringe because of the rapid hydrolytic effect of the blood cholinesterase upon the acetylcholine. Later, at a suitable moment, the injection of acetylcholine in 1 c.c. of water was made rapidly and the needle was left *in situ* until the end of the experiment some minutes later to prevent disturbance of the patient or distortion of the record. The patient's movements and changes in appearance were noted upon the recording paper as they occurred. The observations made upon the two epileptic patients will be described in detail.

Subject K.—An otherwise healthy man, aged 20, began to have attacks 8 years ago. He had had no convulsions in infancy and there was no family history of epilepsy. He had several attacks each day which occurred before breakfast or late in the evening, his last meal being at 5 p.m. The attacks gradually increased in frequency and for the past 2 years he had been having nine to twelve a day although their incidence was variable. The attacks consisted in a momentary loss of consciousness with a liability to drop anything he was holding, followed by a transient sensation of epigastric discomfort, after which he was again quite normal. Three years ago he began to have attacks of similar type but of greater severity in which he fell to the ground without any tongue biting, clonic movements, or incontinence. When

examined he was having three to six minor attacks each morning and a falling attack about once a week. Electro-encephalography showed a normal record interrupted by short outbursts of spike and wave activity (Fig. 8). They occurred every few minutes in fifteen e.e.g. records taken on different days during three weeks. The longest interval seen between these subclinical attacks was 9 minutes and their greatest frequency was three in a minute on one occasion. These petit mal discharges were not accompanied by any subjective or objective disturbance, although an attempt was made to record a clinical attack before breakfast one day.

An intravenous injection of 25 mgm. of acetycholine given in the way already described caused slight bradycardia 7 seconds after the injection, followed by blushing and a little sweating. The patient (subject K) coughed and had a constricting feeling in the chest, a dry sensation in the throat, and slight substernal discomfort. An e.e.g. was obtained for 5 minutes after the pulse rate had become steady and there was no increase in the number of attacks.

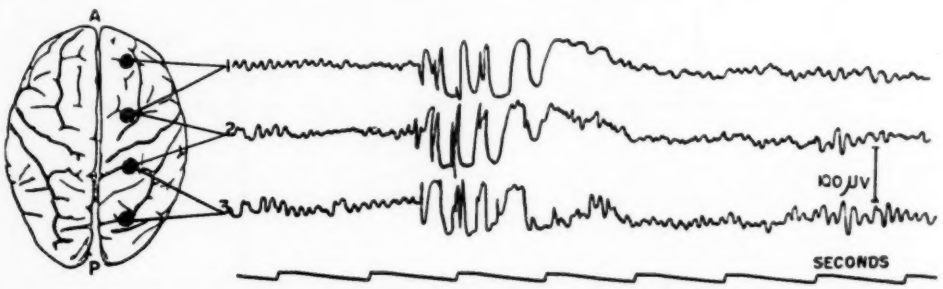

Fig. 8.—Spontaneous subclinical petit mal outburst from the subject used for Figs. 4, 7, and 9.

Fifteen minutes after this first injection 50 mgm. acetylcholine were given under identical conditions. The clinical effect was more marked. In 7 seconds there was an abrupt bradycardia lasting for 4 seconds, with subsequent tachycardia, coughing, flushing of the face, sweating, a constricting sensation in the chest and throat, and slight substernal pain. During the minute following the injection of 50 mgm. acetylcholine there were seven outbursts of epileptic activity of the type shown in Fig. 8. Under no previous circumstances had he had more than three attacks in a minute. The result of this experiment is expressed graphically in Fig. 9.

Ten minutes after this injection of 50 mgm. acetylcholine the same dose was mixed with atropin sulphate gr. 1/150 and given intravenously under identical conditions. There was a very slight clinical reaction with a little flushing and a mild constricting feeling in the chest. There was no increase in the incidence and duration of the epileptic discharges (Fig. 9).

Subject T.—A healthy man, aged 22, began to have attacks 2 years before the experiments. He had had no infantile convulsions and there was no epileptic family history. He became aware of the attacks at work, where he would walk into machinery for no apparent reason. At first he had one attack every few days, but they slowly became more frequent until he was having two to three a day. They always occurred in the day time, were precipitated by going from light into dark, and could be induced sometimes by closing his eyes tightly.

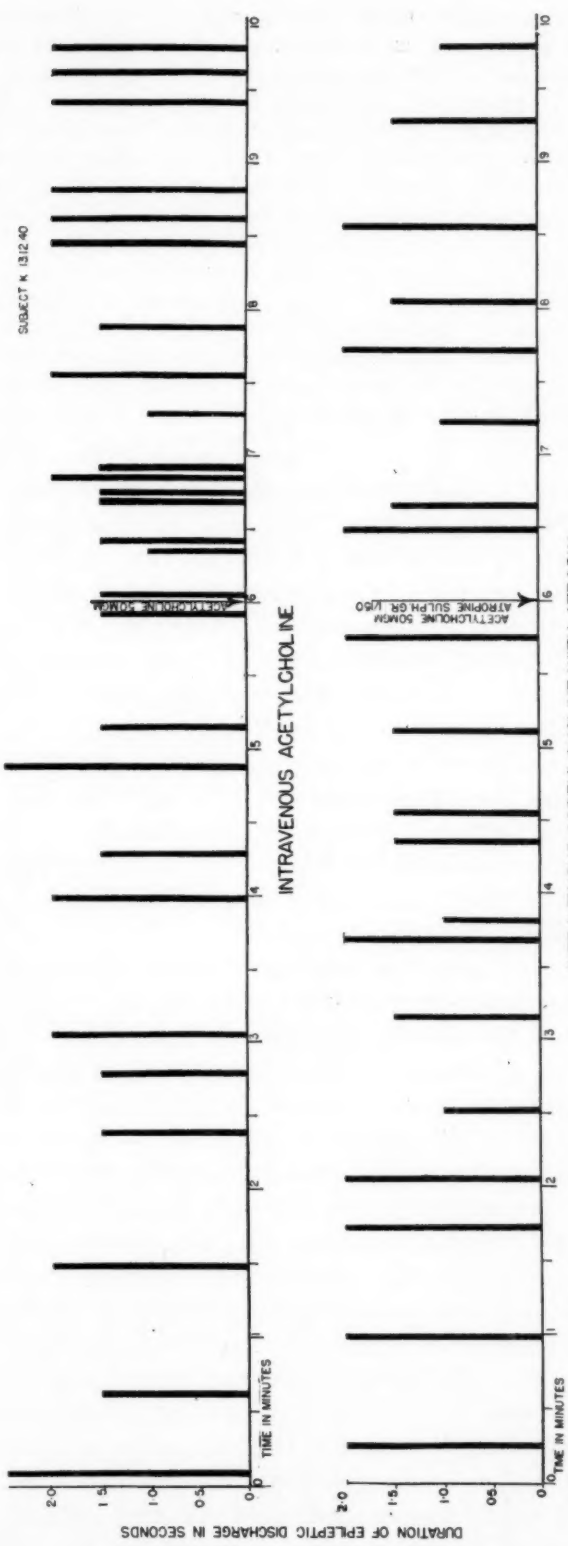

Fig. 9.—The effect of intravenous injection of 50 mgm. of acetylcholine upon spontaneous petit mal attacks seen in the e.e.g. The record is continuous and reads from left to right. Each vertical line represents an attack, seven of which occurred in the first minute after injection of acetylcholine. There is no similar effect when atropin 1/100 gr. is injected after the same amount of acetylcholine under identical conditions.

The attacks were not noticed by others unless the patient was talking to them at the time. He would look vacant and make quite irrelevant remarks such as, " It's over there," or " Why do you do it," in rather an aggressive manner. After a few seconds there would follow a period of confusion lasting for about a minute. He had never bitten his tongue, been incontinent or had clonic movement in an attack. The patient states that he is first aware of a blurred light in the right upper temporal quadrant and that after this has lasted for about 2 seconds he loses touch with his surroundings. He is aware that he is having an attack, and is usually able to force himself to continue what he is doing. He can hear words spoken to him but cannot appreciate their meaning. Similarly he knows that he has spoken, but not what he has said. He has sometimes spilt his tea in an attack and recently fell down in a fit when emerging from a brightly lit cinema into the outside darkness. Electro-encephalography showed scattered abnormal slow waves of low voltage, without any evidence of epileptic activity. No attacks could be induced by closing the eyes, by shining lights and then plunging the room into darkness, or by hyperventilation, nor were any seen in records obtained on three subsequent days.

The patient (subject T) was intelligent and co-operated admirably. The experimental procedure was identical with that adopted throughout. An injection of 60 mgm. acetylcholine was made rapidly into an arm vein, and the characteristic effects of injections of acetylcholine were observed. There was an asystole lasting for nearly two seconds which began abruptly 7 seconds after the injection, with coughing, flushing, sweating, and restlessness caused by discomfort and anxiety. Afterwards the subject described a substernal pain of anginal type, a constricting feeling in the throat, an uncontrollable desire to cough and a sensation of blushing and warmth. He was unable to say whether he had experienced the sensations associated with an attack, for he was too preoccupied with the substernal discomfort to notice this. The e.e.g. was partly obscured by movement artefact but it clearly showed abnormal large slow waves for short intervals. There were no similar outbursts in a 15 minute control period before the injection was made.

The following day an e.e.g. and electrocardiogram were recorded in conditions identical with those in the preceding experiment, and electrodes were also used to record muscular movements to simplify the interpretation of the record. A record was made for 15 minutes without evidence of epileptic activity. The intravenous needle was introduced, a further control period was recorded and without the knowledge of the patient 30 mgm. acetylcholine were injected rapidly. From notes dictated during the experiment and from detailed correlation of the patient's story afterwards the following account of the effects of the injection was obtained. About 7 seconds after the injection the patient was aware of the aura of lights in the right upper temporal quadrant. This increased in intensity for about 2 seconds, and after this the subjective attack commenced. He described this as a sensation of his environment receding rapidly and of his losing touch with reality. The patient's verbatim report reads: " The attack started and I had just time to think ' Is it going to get worse or will it stop? ' Then it became worse and at the same time I felt the pain in the chest. The time that I was beginning to lose touch with things coincided with the pain, and I think that the attack would have passed off if the pain had not come. . . . When I was out I heard someone passing remarks and just remember the

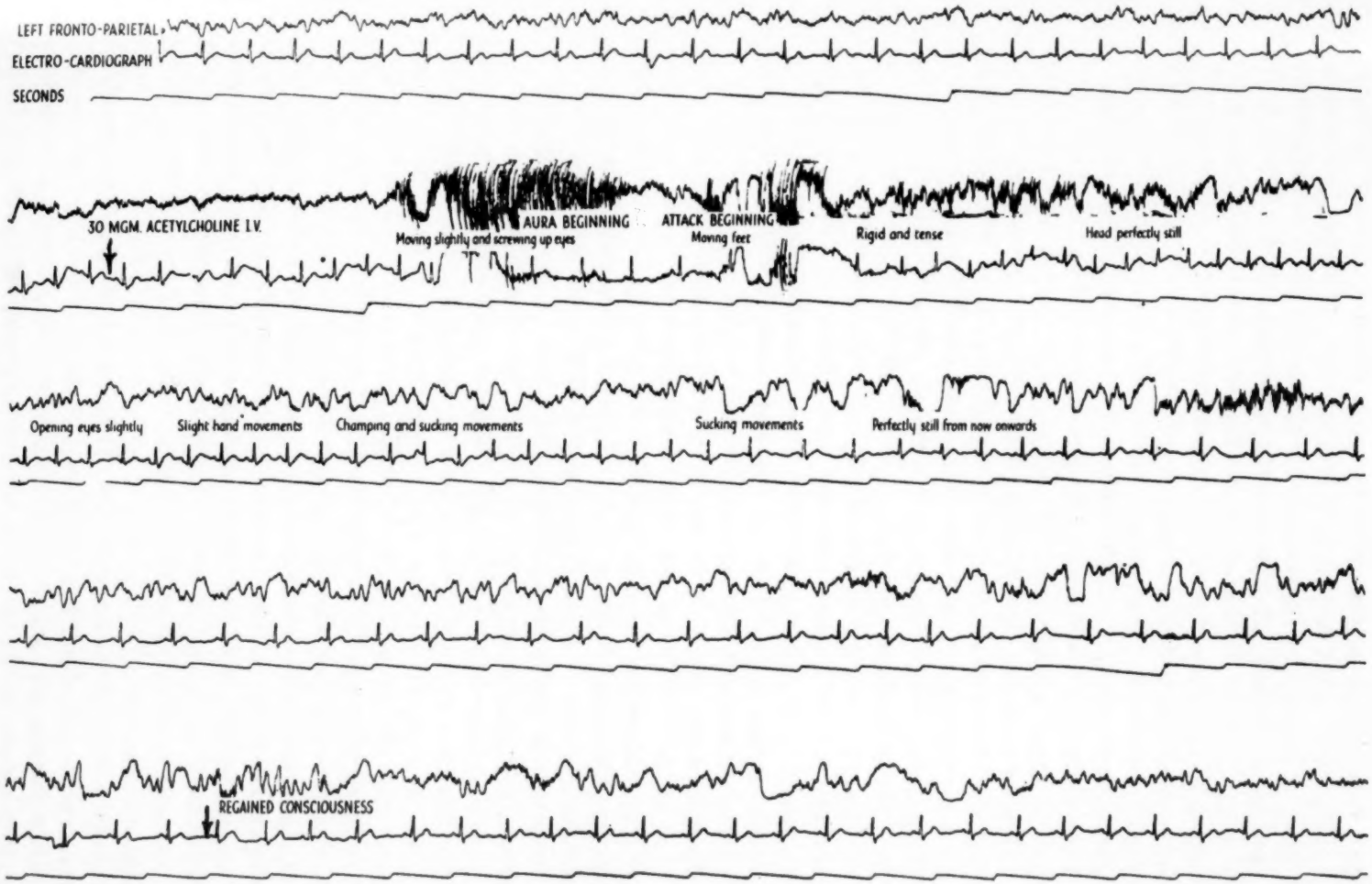

Fig. 10.—An e.e.g. recorded from the left fronto-parietal region of an epileptic subject. Intravenous injection of 30 mgm. acetylcholine was followed by an attack. The exact time of onset of the attack cannot be stated, but the large slow waves seen in the e.e.g. were associated with unconsciousness and co-ordinated semipurposive movements such as are seen in psychomotor epilepsy. Time is in seconds, the long signal representing the end of a minute.

words ' mouth moving,' the next I heard was ' coming out.' " The sequence of these events had been printed on the e.e.g. record reproduced in Fig. 10. The changes observed in the patient were as follows. After the injection he lay still for 6 to 7 seconds. He then screwed up his eyes and shortly afterwards his face became flushed. Except for small movements of the feet he was still. Automatic smacking movements of the lips and tongue followed, and his expression became tense and anxious. His hands gripped the edge of the bed, but after about 30 seconds he relaxed and remained passive until the observations were completed. There was transient flushing of the face, the patient coughed once and there was slight substernal discomfort. The e.e.g. (Fig. 10) showed a resting record consisting of scattered abnormal waves with a frequency of three to five a second and a low voltage, which were rapidly replaced by large slow waves after a burst of muscle action potentials caused by closing the eyes tightly. These waves persisted throughout the subjective attack and for about 10 seconds afterwards. They then ceased abruptly and the record was indistinguishable from that in the control period. There was negligible bradycardia. The patient's attacks, with automatic actions, speech and a sense of dissociation from his environment, are of the type grouped as " psychomotor " epilepsy and the simultaneous disturbance seen in the e.e.g. is known to occur in this type of fit, whereas it is never found in grand mal or petit mal. It should be observed that repeated records obtained both before and after this experiment did not show any evidence of epileptic activity.

At a later date an intravenous injection of 60 mgm. acetylcholine and 1/150 gr. atropin sulphate in 1 c.c. of sterile water was made under experimental conditions identical with those established previously. There were slight subjective effects of the injection, which the patient thought a little less apparent than after 30 mgm. of acetylcholine injected alone. There was no cough or restlessness, and very slight momentary bradycardia. No aura or symptom of an attack occurred and the e.e.g. did not show any change.

The above experiments may be summarized as follows: Intravenous acetylcholine was given six times to two patients who had petit mal and psychomotor epilepsy. 25 mgm. did not cause an attack, but 30 mgm., 50 mgm., and 60 mgm. were all followed by attacks similar to those usually experienced by the patient. When 50 and 60 mgm. of acetylcholine were injected with atrophin sulphate 1/150 gr. there was no evidence of any increase in epileptic activity.

To control these observations the following experiments were carried out: Six injections of acetylcholine in doses ranging from 30 to 60 mgm. were made in normal subjects in experimental conditions identical with those already described. There were the usual sequelæ of the injections, the intensity of which varied from subject to subject, but no evidence of any epileptic discharge was seen in the e.e.g.

Atropin.—The effective dose of atropin necessary to reduce the number of subclinical and clinical epileptic attacks is variable, and it has been common clinical experience that belladonna has a marked anticonvulsant effect in some epileptics and not in others. In this series of experiments atropin sulphate was used to minimize the parasympatheticomimetic effect of eserine and prostigmin,

but 1/150 gr. and even 1/100 gr. subcutaneously were found insufficient to modify the effect of these substances upon the incidence of epileptic attacks. When 1/100 gr. was injected subcutaneously alone in two instances it reduced the number of attacks and when injected intravenously with acetylcholine or subcutaneously with carbaminoylcholine chloride it completely abolished the epileptogenic effect of these substances (Figs. 7 and 9).

Histamine.—As it was possible that acetylcholine might cause an increase in epileptic activity by modifying the cerebral blood flow (Wolff, 1929) histamine acid phosphate 0·1 mgm. was injected intravenously in two epileptic patients from whom subclinical attacks were being recorded by e.e.g. There were the usual symptoms of headache, flushing, and tachycardia (Pickering, 1933) but there was no change in the incidence of epileptic cerebral discharges. From these observations it appears that cerebral vasodilatation is not alone responsible for the changes induced by acetylcholine, and that the subjective effects of the injections do not necessarily give rise to an increase in epileptic activity. The first conclusion is supported by the observation that CO_2 causes a profound cerebral vasodilatation in man (Carmichael, Doupe, and Williams, 1937), although it suppresses petit mal activity (Lennox, 1928).

Pilocarpine.—To determine whether the increase in epileptic activity resulting from injection of acetylcholine was due to peripheral activity of the parasympathetic system pilocarpine nitrate 1/10 gr. was injected subcutaneously in two epileptic subjects who showed subclinical epileptic discharges upon the e.e.g. There was salivation, flushing, and sweating, but no change in the incidence of the epileptic discharges was noted.

Apomorphine.—In some of the subjects increase in epileptic activity after eserine and prostigmin was associated with nausea, abdominal discomfort, and even vomiting, and it was possible that these symptoms were causally related to the epileptic activity. Similar symptoms were therefore produced by an injection of apomorphine hydrochloride 1/10 gr. in two epileptic patients who showed subclinical attacks upon the e.e.g. There was no increase in the epileptic activity in either case.

Discussion

The outbursts of cerebral electrical activity associated with epileptic attacks are sharply delimited and fall into groups having characteristic rhythmical wave patterns which are easily recognized on the e.e.g. The size and duration of the outbursts are related to the severity of the clinical attack and their form can be correlated with the clinical types of epilepsy (Gibbs, Gibbs and Lennox, 1937). Although the different groups are distinct they may appear in mixed forms in the same subject. This communication is primarily concerned with the disturbance associated with petit mal, which has many well recognized features. In this, as in the other forms of epilepsy, cerebral electrical discharges known as subclinical attacks are frequently seen in the absence of any demonstrable alteration in consciousness. They have a form identical with that seen in a clinical fit, but they have a lower voltage and a shorter duration. Subclinical fits often occur at short intervals, even when the clinical fits are

infrequent, and as in any one subject the ratio of clinical to subclinical fits is fairly constant it follows that they offer a rapid method of observing the effect of drugs upon epilepsy. The incidence and duration of subclinical attacks have been used by Gibbs, Lennox and Gibbs (1940) to investigate the effects upon petit mal epilepsy of changes in various blood constituents and of blood *p*H. In subjects with petit mal, in whom spontaneous attacks are infrequent, subclinical attacks may be induced by over-breathing, and the application of this fact to the present investigation has already been described (Williams and Russell, 1941).

There has recently been increasing interest in the effect of cholin-like substances upon the activity of the central nervous system. Acetylcholine is present in the grey matter (Stedman and Stedman, 1939) and it is liberated when the isolated brain is perfused with eserinized blood (Chute, Feldberg and Smyth, 1940). Some workers have reported liberation of acetylcholine into the cerebrospinal fluid on stimulation of the central cut end of the vagus (Dikshit, 1934), but others have been unable to confirm this (Adam et al, 1938). Schweitzer, Stedman and Wright (1939) found that prostigmin as well as acetylcholine and allied substances have a direct inhibitory effect upon the reflex activity of the spinal cord, while eserine on the other hand increased the reflex activity and caused convulsive movements (Schweitzer and Wright, 1937). Bremer (1938) introduced acetylcholine into the carotid artery in rabbits and found that minute doses increased the size and frequency of the waves of cerebral electrical activity and that larger doses depressed them. Miller (1937) applied eserine to the exposed cortex in dilute solutions and obtained an increase in the muscular rigidity of the corresponding limb. He thought that the effect was specific and was caused by an enhancement of cortical synaptic transmission. Miller, Stavraky and Woonton (1940) amplified the experiments and produced a reduction in the size of the waves of electrical potential change by acetylcholine applied locally. They enhanced the effect with eserine and abolished it with atropin, and consequently think that acetylcholine may facilitate cerebral synaptic transmission. More recently McKail, Obrador and Wilson (1941) have produced changes in the responses to electrical stimulation of the cortex by intra carotid injection of similar substances.

It was in view of these observations that the effect of some of these substances upon the cerebral electrical discharges seen in epilepsy were investigated. The results described in the present paper seem to fall into line with the observations already reported (Williams and Russell, 1941), that a small subcutaneous injection of eserine decreases petit mal activity and larger doses increase it, while prostigmin invariably causes an increase in petit mal. The different actions of eserine and prostigmin are analogous to those obtained upon the reflex activity of the spinal cord by Schweitzer and Wright (1937). Schweitzer, Stedman and Wright (1939) suggested that as eserine is a tertiary ammonium base and is fat and water soluble it might enter the nerve cells and cause changes there, while prostigmin, a quarternary base, is only water soluble and acts outside the cell, perhaps in the synapse. This explanation raised the possibility that the effect of eserine and prostigmin upon epilepsy might be central in origin.

That injections of eserine, prostigmin, carbaminoylcholine chloride, and acetylcholine have a similar action upon epilepsy, and that this action is inhibited by atropin, suggests that the changes are related to an alteration in the (acetylcholine transmitting mechanism somewhere in the body. However it is caused, the effect may be an indirect one due to peripheral changes, or it may be directly due to alterations in the central nervous system. The changes to which cholin-like substances give rise in the intact organism are so widespread and complex that it is difficult to single out the factor causing changes such as have been reported in this paper. Coincidental changes which might have been responsible are:

(1) an alteration in respiratory exchange through bronchiolar constriction or respiratory rate modifying the arterial CO_2 or O_2.

(2) a rise in blood *p*H by glandular secretion, especially that of HCl into the stomach, resulting in an increase in petit mal activity (Nims et al, 1940).

(3) a change in blood sugar level from adrenal or pancreatic stimulation (Hrubetz, 1937) ; and

(4) an alteration in cerebral blood flow, either an increase through cerebral vasodilatation (Wolff, 1929) or decrease through fall in systemic blood pressure (Wolff and Cattell, 1935).

Each of these changes, but especially an increase in blood *p*H or a fall in blood sugar, might increase petit mal activity.

Respiratory exchange was measured and found to be surprisingly constant under the conditions of the experiments, and any changes which occurred bore no relationship to the incidence of epilepsy. Similarly, the small alterations recorded in the blood sugar levels (Figs. 3 and 4) were not related to the changes in epileptic activity. The injections of acetylcholine were followed so quickly by an increase in epileptic activity in subjects K and T that neither blood *p*H or sugar changes could have had time to be effective. Suggestive evidence that the changes were not caused by alterations in blood *p*H has already been advanced (Williams and Russell, 1941), but the only conclusive proof is determination of the actual blood *p*H during the experiments. No observations of the effect of cholin-like substances upon the blood *p*H have been reported, so that a direct coupled amplifier and a glass electrode system is at present being used for this purpose.

Evidence has been produced that epilepsy might be related to an alteration in local cerebral blood flow (Penfield, 1938). Acetylcholine produces both an increase in cerebral blood flow by cerebral vasodilatation, and a decrease by diminished cardiac output. CO_2 increases cerebral blood flow enormously (Carmichael, Doupe and Williams, 1937), but it prevents petit mal epilepsy, and in the present experiments histamine did not have the same effect on epilepsy as did acetylcholine, although it is an efficient cerebral vasodilator. No cerebral symptoms have been described after injection of acetylcholine in the absence of very prolonged asystole (Carmichael and Fraser, 1933), and in the present experiments there was bradycardia but never asystole for longer than 2 seconds. Furthermore, the same dose given to normal subjects was not associated with

any electro-encephalographic changes characteristic of cerebral anæmia or anoxia. Fig. 10 shows that the cardiac slowing is very slight in the presence of a clinical attack. Carmichael and Fraser (1933) reported the occurrence of a grand mal fit in a normal person after intravenous injection of acetylcholine, but this fit was preceded by a period of asystole lasting for 11·8 seconds.

As the arm-tongue circulation time usually ranges from 13 to 19 seconds, with a low level of 10 seconds (Kremer and Robertson, 1935) the extremely rapid onset of an aura after intravenous acetylcholine shown in Fig. 10 suggests that the attack had begun before the acetylcholine had reached the cerebrum, but the continuation of the effect seen in this figure and in Fig. 9 may have been due to cerebral changes.

The slow waves associated with petit mal may be transmitted across the cortex by neurone chains in such a manner as that described by Adrian (1936) for their rate of propagation is slow, or the rhythmic activity may be spread throughout the hemispheres by a strictly electrical mechanism which is independent of any neuronal co-ordination of cellular activity (Gerard and Libet, 1940). Similar slow waves caused by co-ordinated beats of cell masses in response to introduced substances can spread through cerebral tissue in which the appropriate nerve pathways have been severed (Garard and Libet, 1939), but nothing is known about the physico-chemical mechanism causing the initiation, persistence, spread, or cessation of the rhythmic electrical activity associated with epileptic attacks. The present observations may be interpreted in terms of synaptic transmission, but there is at present little justification for applying this directly to the abnormal central mechanism responsible for epilepsy.

Summary

Acetylcholine and allied substances were administered to patients with petit mal epilepsy. Electro-encephalographic records were made of clinical and subclinical attacks, both spontaneous and induced by overbreathing. Intravenous injection of acetylcholine was followed by an increase in the recorded epileptic activity. This action ofacetylcholine was inhibited by atropin, and other substances having somewhat similar pharmacological effects did not alter the incidence or duration of the attacks. No similar results could be obtained in normal subjects.

Experiments were performed in an attempt to elucidate the mode of action of acetylcholine in modifying epilepsy, and several of its peripheral effects were excluded. The results are discussed in relation to recent work upon the effect of cholin-like substances on the central nervous system.

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A CRITICAL REVIEW

DEMENTIA IN MIDDLE AGE

BY

W. H. McMENEMEY

Introduction

WHEN a middle-aged person is presented for examination because of symptoms of developing dementia, the physician is faced with an interesting, and often an exacting, problem in differential diagnosis. It is proposed to discuss the causes of progressive dementia in such persons and at the same time to make observations from the clinical and pathological viewpoints concerning the individuality of certain of these diseases.

The Import of " Presenile Dementia "

The use of the word " presenile " as applied to dementia does not connote a senile ætiology but merely a period of life. Nevertheless, partly, no doubt, because of the similarity of the histologies of Alzheimer's disease and senile dementia, the term appears to be regarded by not a few in a way which presupposes senescence as an ætiological factor: thus, such patients are sometimes said to be " suffering from senility before their time." This not uncommon misapprehension tends not only to segregate these diseases (" the essential dementias of the presenium "), of which the age incidence is characteristically in the presenium, but also to obscure their true place in the hegemony of neurological disorders. How far, in point of fact, senescence is implicated in these diseases remains to be seen.

The presenium or middle age is usually understood to include the years from forty to sixty, but some would extend the upper age limit to sixty-five. One is aware, however, of differences in ageing as seen in various individuals and families: some persons are senescent by sixty whilst others are still middle-aged in body and mind when they have reached " the allotted span." The saying that a man is as old as his arteries is a generalization which finds some confirmation in the histology of the ageing brain. That years alone do not age a man is well exemplified in that extreme instance of precocious senescence to be found in progeria: such subjects may be senile, in all respects, in childhood. The presenium and senium are but arbitrary epochs and no hard and fast dividing line can be made between them. It was the desire to distinguish between Alzheimer's disease and senile dementia which led to the specialized conception of the presenium.

A careful study of the patient's history and present condition, together with cursory acquaintance with the immediate relatives, will suffice to show whether he or she has entered the senile period of life. The essence of a presenile dementia, if the term is to have any significance at all, is that the mental illness has begun at a time when the patient still retains normal vitality of body and mind.

It is unfortunate that the term " presenile dementia " has, for some people, come to be but a synonym for Alzheimer's disease or Pick's disease, for there are many other causes of dementia in middle-aged subjects. Reviews on " presenile dementia " have been made by Kehrer (1925), Runge (1930), and by Schottky (1932). In recent years, also, there have been two discussions at the Royal Society of Medicine (Critchley *et al*, 1933; Mayer-Gross *et al*, 1938) which have served to indicate the scope of this concept of " presenile dementia," but Critchley at the outset stressed the fact that for the neurologist it usually offered itself as a problem in differential diagnosis. The first discussion provided an excellent account of the " essential presenile dementias," while the second, although largely confined to a psychiatric analysis of the symptomatology, did give a further and clear reminder of the variety of diseases to be met with in this group.

It is clear, therefore, that the term " presenile dementia " can have only a clinical meaning for provisional use while the diagnosis is as yet unsettled, and that when a patient in this age-group presents symptoms of intellectual deterioration the temptation to label the case as one of the essential dementias of the presenium should be resisted until all the other theoretical causes have been reviewed; only in this way is it possible to avoid overlooking a cerebral tumour with unusual symptoms and signs.

It has been suggested that the presenile group of dementias be divided up into two, primary and secondary; the latter includes those of known ætiology —for example, tumour, syphilis, or arteriosclerosis—while the former category is reserved for the diseases of uncertain ætiology. Such a classification, although based upon our present state of ignorance, appears to be the only one possible at present.

It has been customary to retain the use of the term " presenile dementia " for the small numbers of cases which owe their origin neither to tumour, trauma, infections, nor arterial disease, but which are the " primary " or " essential " dementias of the presenium. These diseases, which are of particular interest, are generally believed to be rare, for they are infrequently reported and their nature is at present imperfectly understood. Being placed between the well-defined insanity of adolescence and the familiar dementias of old age, and being readily confused with other involutional psychoses, these maladies often pass unrecognized during life whilst they are overlooked not infrequently at autopsy.

Dementia implies a disturbance of function of the cortical cells of the brain, although in not a few instances subcortical or other cells may be primarily responsible for the symptoms (Putnam, 1939). This disturbance of function may, or may not, be accompanied by a morphological alteration of the cells.

The earliest signs of dementia vary little, whatever be the underlying pathological cause: they amount to an alteration in the personality, so that the patient's friends notice in him a certain lack of initiative, or maybe an irascibility, a facileness or a lack of interest which is foreign to his nature. His mood will be determined largely by his previous personality, but in general it has been said that presenile dementias are characterized by depression rather than excitement. A paranoid trend may be detected as an early symptom in one who has shown this pattern in his previous psychological make-up. As the disease develops it soon becomes apparent that the mind is being deranged concurrently in cognitive, affective, and conative aspects. The attention becomes readily distractable, and the patient develops a memory defect, at first for recent happenings, and this may show itself as forgetfulness when writing (missing of letters and words), or as a disorientation in time or even place, becoming more and more noticeable as the illness progresses. The disordered action of the mind, and especially the disturbed effect, may find expression in conduct which lacks the control of reason, so that perseveration, stereotopies, and verbigeration may be prominent symptoms. Although the amount and type of motor unrest which may characterize a presenile dementia vary considerably in different cases, some degree is to be expected in most, and an explanation has been offered for this fact by postulating that this activity is but the expression of the victim's reaction to the abnormal state of his brain. The final stage of dementia is one of complete apathy, intellectual dullness, failure of all memory, and loss of sphincter control. The march of dementia has this general pattern irrespective of the determining pathology. Nevertheless, some dementing diseases have symptomatologies which are more or less characteristic and are of help in diagnosis. The early stage of dementia may be readily obscured by, and sometimes simulated by, the confusion which accompanies a severe toxæmia, by dysarthria, paraphasia, or mutism.

The diseases which may manifest themselves in middle age and give rise to symptoms of dementia are many. In not all of them does the dementia become profound. In reviewing the causes of " presenile dementia " it is convenient to consider first the so-called " primary " group.

So-called Essential Dementias of the Presenile Age-group

There are two diseases associated with the names of Alzheimer and Pick respectively which are usually regarded as constituting this group. Sometimes, however, the term " presenile dementia " has been used as a synonym for Alzheimer's disease.

Alzheimer's disease.—The recognition of this condition dates from 1907, when Alzheimer described it for the first time. Since then some hundred or more instances of the disease have been reported, but probably very many more have been overlooked whilst not a few have been recognized but not reported. It seems likely, in point of fact, that the disease is not uncommon. Histologically, there are changes of the type seen in senile dementia, but they are more severe. Thought at one time by Fuller (1912) to be but a senium præcox, the

revolt against this view was led by Barrett as long ago as 1913 as the result of a critical histological analysis of a case dying at the age of thirty-one. Since then other examples of the disease have been described in persons under the age of forty, and Lowenberg and Rothschild (1931) have recorded the case of a woman who, several years after the beginning of the illness, gave birth to a healthy child. Although it is classically a disease of middle age and onwards somatic manifestations of senility are rarely present. On the contrary, Malamud and Lowenberg (1929) have described an example commencing at the age of seven, after scarlet fever, and proving fatal within sixteen years. At autopsy, the histological findings were typical of Alzheimer's disease, but, in addition, there were extensive degenerative processes in the choroid plexus. Their conclusion is that, ætiologically, the clinicopathological syndrome which we know by the name of Alzheimer's disease may be caused by a variety of factors. We are, as yet, entirely in the dark as to the nature of these; we conjecture that they are toxic or degenerative in origin, producing results in the cerebral parenchyma similar to those which we associate with a type of dementia found in the elderly. The impression is gained in examining cases of Alzheimer's disease histologically that some of them are in keeping with what Fuller called " senium præcox," whereas others suggest the visitation of some cataclysmic agent, so great is the extent of the process: these two extremes may approximate to the intrinsic and extrinsic forms of the disease which we believe exist.

There are certain examples of the disease which have shown a familial character (Lowenberg and Waggoner 1934; McMenemey, Worster-Drought, Flind and Williams, 1939). The first of these concerned a father and four out of his five children. The other instance was a man, in the previous generation of whose family three out of four siblings were afflicted with a similar disease. In both of these studies it came to light that there had been first cousin marriages in the parents. It should be added that the evidence for the familiar character in these cases is circumstantial, as in each instance the brain of only one afflicted member of the family has been examined histologically. It is certain, however, that the clinical illnesses were always similar, and there is a record of an incomplete examination of a brain in one member of the family described by Lowenberg and Waggoner which is highly suggestive of Alzheimer's disease. Schottky's (1932) family with presenile dementia may have been an instance of Alzheimer's disease, although the author favoured the diagnosis of Pick's disease: only the naked eye findings are mentioned. In addition, there are other examples where a family history is suggestive (von Braunmuhl, 1932; Rothschild, 1934), whilst Lowenberg (1937) quoted an example of a man with Alzheimer's disease whose father had had senile dementia. In view of the anatomical similarity of these diseases it should be mentioned that Meggendorfer (1926) and Weinberger (1926) both believe that heredity plays some part in senile dementia, but Grunthal (1936) maintains that nothing concrete can be established on this score. The late age of onset of senile dementia must, of necessity, make it difficult to obtain a family history. It has, however, been described in twins (Scheele, 1933).

It would seem premature to press for an heredodegenerative outlook

on Alzheimer's disease in view of the relatively few reported instances of a familial incidence, but it seems not improbable that some cases owe their origin to an abiotrophic tendency sufficiently definite to be brought into play by a minimum of extrinsic influences. The reported examples of this disease occurring under the age of forty (Perusini, 1910; Barrett, 1913; Urechia and Danetz, 1924; Malamud and Lowenberg, 1929; Struwe, 1929; Schottky, 1932; Kufs, 1937) are more readily explained in this way. The last of these cases had, in addition to the characteristic findings of Alzheimer's disease, sclerosis of the olivary bodies and atrophy of the basal ganglia, findings not easy to explain unless the abiotrophic view is accepted.

It would seem best to regard Alzheimer's disease as a psychosis of middle age which has a histological picture similar to but usually more extensive and severe than that of senile dementia. The last word remains to be said on the relationship of these diseases to one another. Wilson (1940) would group them together, regarding the pathological arrangement as preferable to the clinical. Whilst it is difficult to exclude senility as a factor in the ætiology of senile dementia, it is worth a thought that there are other senile psychoses, as, for instance, the type described by Claude and Lhermitte (1910), which lack the recognized histology of senile dementia: in many cases of Alzheimer's disease, however, it appears equally improbable that senility could be reckoned as a factor in ætiology, although abiotrophy or " premature local decay " could be accepted without cavil. The Růžička-Grünthal biological hypothesis, however, to which reference is made later, allows of both extraneous toxic factors and either senility or abiotrophy being concerned.

Clinically, we know Alzheimer's disease as a progressive dementia with a course, on the average, of from two to five years, occurring typically in persons between the ages of forty and sixty and usually in the absence of arterial disease. There is nothing unusual about the dementia except that eventually it becomes profound and is usually associated with emaciation. It is preceded by a characteristic phase of great excitement, restlessness, and confusion. Rothschild and Kasanin (1936) have described the reactive symptoms as " an attempt at rejuvenescence in face of an abnormal ageing process." There may be involvement of either the pyramidal or extrapyramidal motor system, or both, and epilepsy is not unusual, especially late in the course of the illness. Loss of memory for recent events is not infrequently the first symptom which brings the patient to the physician's notice. According to Boyd (1936) the early intellectual failure which characterizes this condition is more in the nature of a loss of co-ordinating function and a narrowing of the ability to perform in several fields at once. When it is recalled how widespread are the histological changes it is not surprising that the dementia becomes extreme; neither is it unexpected that the symptomatology can vary, depending upon the march of the process; in some cases, for instance, aphasia may be an early and prominent sign. Occasionally the disease appears to become arrested. Sometimes focal symptoms are marked, and at autopsy the atrophy may be so unevenly distributed as to suggest Pick's disease.

The characteristic histological picture, apart from atrophy of the nerve

cells, is the presence of " senile plaques " in great numbers and of the " neurofibrillary change of Alzheimer." Neither of these findings is pathognomonic, and authenticated instances of the disease are known in which plaques alone were present: Alzheimer himself published a case of this nature, the distinguishing feature being the presence of large plaques. Senile plaques, therefore, are invariably present in this malady, and if the case is long-standing they may be very numerous. They are found in the grey matter of the cortex, especially in the second and third laminæ of the frontal and occipital regions and of the hippocampus. They are less plentiful in the pre- and post-central gyri. They may be found in the basal ganglia and cerebellum. In old-standing cases the cortical grey matter may be almost entirely occupied by these curious structures. They are recognized in silver impregnated sections as irregular-shaped masses measuring up to 100μ in diameter; around the dark centre, which may give the chemical reactions for amyloid, are numerous club-like masses radiating outwards and bearing a superficial resemblance to actinomyces. With suitable modifications of the silver technique microglial cells can be demonstrated in the substance of the plaque, and farther out in the periphery lie astrocytes which have largely undergone fibrous transformation. Von Braunmühl (1932) believes their origin to lie in a densification of the ground substance. This, again, is in keeping with the hypothesis of Růžička (1922, 1924) who maintains that, with advancing years, or on account of illness, there is a tendency for the colloids of the body to aggregate into larger particles and to precipitate out. To this phenomenon the name of " protoplasma-hysteresis " is given, and it represents the third biological process, the other two being assimilation and dissimilation. The senile plaque does not appear, as yet, to have been described in animals. There are, however, certain other structures met with from time to time which resemble senile plaques. A case described by Gerstmann, Straüssler, and Scheinker (1936) concerned a twenty-six-year-old female who died of a cerebellospinal degeneration which had been transmitted as a dominant through several generations. At autopsy curious incrustations were found in the cortex, especially in the superficial layers, the basal ganglia, and the white matter, which had some resemblance to senile plaques. They are figured as being numerous in the molecular layer of the cerebellum. Their distribution is unusual for senile plaques, and certainly they seem to differ from these in several respects. In addition there are the so-called fatty plaques, which have been described also in animals (Rizzo, 1924) and various " metabolic " and " myelin " bodies which have been reported in adult forms of Schilder's disease. Yet another type of " pseudoplaque " was seen in an unusual familial presenile dementia reported by Worster-Drought, Greenfield, and McMenemey (1940); these structures were mostly in relation to blood vessels.

The second histological feature of Alzheimer's disease is the presence of irregularly thickened neurofibrils, usually bent and twisted so as to justify the use of the terms " tangles " and " loops." Recent studies by Alexander and Looney (1938) suggest that these structures are " hypermineralized." Although characteristic they may be scanty or even absent, but as a rule they constitute

a striking feature of the histology. Bouman (1934) regarded this change as an example of "hyperdifferentiation" similar to that which may occur after injury. Although the thickened neurofibril may represent an attempt at healing there is every reason to hold that any such attempt fails in its purpose. It is impossible to believe that a nerve cell showing such a change in the structure of its neurofibrils, even making allowances for the fact that the change which we see is in autopsy or biopsy material after fixation and impregnation, can be able to function in its usual way, and one presumes that such a cell is already effete. Bouman's theory was applicable to all the changes seen in this disease and in senile dementia, namely senile plaques, "torpedoes," and dendritic swellings. It would seem right to regard them as all of the same order and the Růžička-Grünthal hypothesis can be applied as readily to the neurofibrillary change as to the senile plaque. The latter concerns the "ground substance" whereas the former implies a more devastating process involving the nerve cells as well. This explanation will account for the fact that the senile plaque is characteristic of senile dementia whereas the neurofibrillary change is most familiar in Alzheimer's disease (Critchley, 1930), and also for the fact that although plaques not infrequently occur in the absence of the alteration in the neurofibrils the converse is probably unusual, if not unknown. It presupposes a greater likelihood of the impoverished ground substance being first concerned in the more benign senile dementia, whereas in the younger subject the highly organized neurone succumbs first to the more malignant Alzheimer's disease.

Although both the plaques, and more especially the neurofibrillary alterations, are less numerous in senile dementia, Grünthal (1930) has stressed the fact that in some cases it may be impossible to tell the two diseases apart. Indeed it may well be that the differences both in symptomatology and histology between these two diseases may be no more than can be accounted for by the fact that in Alzheimer's disease the patient is younger and therefore better able to resist the onset of the illness. In Alzheimer's disease there is a rough parallelism between the number of plaques and neurofibrillary alterations; but a quantitative estimation of the former is no true guide to the severity of the symptoms although it is some index of the duration of the disease. If the neurofibrillary alterations are much in excess of the senile plaques it suggests that the illness is of relatively short duration and that it is a malignant form.

Although the association of senile plaques and neurofibrillary alterations in a presenile subject is strong evidence of Alzheimer's disease, Rothschild and Kasanin (1936) insist that, before the diagnosis can be established, the clinical findings must also be typical. These authors have described examples of toxic psychosis with the histological characteristics of Alzheimer's disease which they are not prepared to accept as instances of the latter. It would seem feasible, however, to regard such cases as instances of Alzheimer's disease which have been precipitated by reason of an acute illness. Such cases, in fact, approximate more to the "extrinsic" type of case than to the "intrinsic" or "pure" abiotrophic variety.

Neuburger and Braunmühl (1930) instance a man of fifty-six with a traumatic

dementia dating back to the age of twenty-two whose brain showed an abundance of senile plaques. More recently Claude and Cuel (1939) have described the case of a female who died of a dementia, at the age of fifty-seven, seven years after an accident. Histologically the lesions are said to be typical of " senile dementia " with both senile plaques and neurofibrillary alterations. These cases furnish a useful illustration of the frequent co-existence of both abiotrophic tendency and external precipitating factors in the ætiology of this disease.

Vascular alterations in Alzheimer's disease are minimal and are not thought to play any part in its ætiology, although Krapf (1931) has suggested that arterial hypertension requires consideration, especially as a factor predisposing to epileptiform seizures.

Pick's disease.—This term is confusing because it is also applied to polyorrhomenitis; for this reason Nichols and Weigner (1938) prefer to call it " idiopathic circumscribed presenile cerebral atrophy," a comprehensive title which succeeds in describing an average case. It affects principally women between the ages of fifty and sixty, the course of the illness being from two to ten years. It was first described by Pick in 1892, since when some seventy examples have been recorded, the youngest of whom was only twenty-one (Lowenberg, Boyd, and Salon, 1939). It is probably rarer than Alzheimer's disease. Nichols and Weigner (1938), however, believe it to be commoner than is suggested by the number of recorded cases. This view is almost certainly correct, for until recently the only examples reported have been those with frank atrophy of some part of the brain; it seems likely, however, that instances not infrequently occur without much naked eye evidence of atrophy: one such was reported by Bouton (1940).

The atrophy concerns certain of the cortical cells, especially the upper three layers, but Freeman (1933) believes that the process begins in the white matter. Usually the frontal lobes are affected, but occasionally the temporal poles and less often the parietal lobes, are involved. Sometimes a whole hemisphere shares in the atrophy, including the subcortical white matter. Moreover, some authors have noted the involvement of several lobes, or even both hemispheres, whilst others have found the basal ganglia and substantia nigra implicated in the atrophy. It is said that the left side of the brain is involved more often than the right, and this may account for the fact that aphasia is a frequent symptom. The atrophy, therefore, although usually circumscribed may affect practically any part of the brain, and Ferraro and Jervis (1936) stress the fact that histological changes, although most in evidence in the grossly atrophic areas, are diffuse throughout the whole cortex. This observation is in keeping with the clinical description of this disease given by Goldstein and Katz (1937) as a " systemic deterioration of the function of the cortex of the brain." Bouton (1940) remarks on the close proximity of apparently normal cells to those in an advanced stage of chromatolysis even in the most affected areas. Gliosis follows the atrophy, so that the " varying course of the disease is faithfully reflected in the condition of the glial elements " (Bouton). According to Davison (1938) no specific cortical laminæ are concerned in this

disease. Urechia (1930) considers the presence of argentophil corpuscles in the basal parts of the nerve cells to be almost pathognomonic of this disease.

Early symptoms are amnesia, aphasia, akinesia, and a gradual loss of control of the higher cerebral functions. When the frontal lobes are involved the dementia is progressive and eventually profound, although the loss of memory is seldom complete. According to Bouton (1940), however, careful examination will often elicit the fact that the memory is surprisingly intact at a time when it would appear, on less critical examination, to be much impaired. Malamud and Boyd (1940), in discussing atrophy of the temporal lobe in this disease, remark on the type of mental deterioration to be expected: according to these authors it amounts to a reduction in associative power and thinking, in judgment and insight, whereas memory, orientation, and attention remain relatively preserved for some time. Benedek and Lehoczky (1939) find that even if there is severe deterioration of the mind there remains an emotional accessibility. Similar observations have been made by Stertz (1926), Schreider (1927), and von Braunmühl and Leonhard (1934). Goldstein and Katz (1937) comment on the preservation of the active abstract attitude in behaviour. They recommend a critical psychological examination at the stage of the disease when personality has not yet been changed to such a degree that good co-operation and an exact examination are impossible. Schenk (1938) speaks of the importance of a knowledge of the prepsychotic personality in studying these cases. As insight is usually impaired early on in this disease it forms a useful diagnostic point from cerebral arteriosclerosis. There is considerable individual variation in the symptomatology and the duration of the illness, depending, no doubt, upon the site of the atrophy, but the following differential points are usually given to distinguish it clinically from Alzheimer's disease. The age of onset tends to be later, the course is more protracted, epilepsy is rare, and the patient is apathetic and totally lacking in initiative, whereas in the latter disease restlessness is characteristic at some stage in its course. On the other hand, some authors have described a preliminary phase of restlessness in Pick's disease which in some cases appears to have been marked. Nichols and Weigner (1938) notice a resemblance between Pick's disease and general paralysis paralleled by the similarity of Alzheimer's disease to senile dementia.

The ætiology is till doubtful. Gans (1922) was inclined to place this disease in the category of the abiotrophies, because the parts of the brain involved are phylogenetically young. Orari and Spatz (1926), Ferraro and Jervis (1936), and Davison (1938) have disagreed with this assertion of Gans, because the areas concerned have not always been phylogenetically the youngest. On the other hand, Shenk supports the view of Gans. The occurrence of this disease in families appears to strengthen the abiotrophic view and the very nature of the malady is in keeping with our conception of heredodegeneration. Benedek and Lehoczky (1939), in fact, consider that the importance of familial factors in Pick's disease may be taken as-satisfactorily established. In a case described by Thorpe (1932) there was a history of the father having had senile dementia. Grünthal (1922), Braunmühl and Leonhard (1934) and Shenk (1938) have described undoubted familial instances of this

disease and there are others in the literature which, according to Ferraro and Jervis (1936), have not been sufficiently proved. The latter authors do not, however, favour classifying this disease as a member of the heredodegenerative group, and therefore independent of senility, on the grounds that the number of observations is not as yet sufficient to warrant this opinion. They prefer to regard it, with Pick, as a senile process. Although they found only slight vascular changes they noticed an extensive perivascular distribution of the disease, and they postulate repeated localized vascular spasm as the cause of the circumscribed atrophy; they conclude, however, by stating that they are not prepared to say whether angiospasm may more easily affect a predisposed tissue. Davison (1938) found some confirmation for this view in a histological study of his first case. The smaller cortical vessels were frankly sclerotic, but as the patient was sixty-three years of age it is not unlikely that the association was fortuitous. Without in any way detracting from the theory of angiospasm postulated by Ferraro and Jervis (1936), one must admit that the cerebral vessels in this disease appear from a study of the literature to have been singularly free from histological evidence of disease. Moreover, the sex incidence of Pick's disease (and for that matter of Alzheimer's disease also) is the opposite of that of cerebral arteriosclerosis (Rothschild, 1938). It would appear, therefore, that the exact nature of this disease is still obscure, but that reliable evidence exists for regarding it as a heredodegeneration.

With regard to more recent diagnostic procedures, encephalography or ventriculography may furnish good evidence of organic dementia, and the diagnosis of Alzheimer's and Pick's diseases may be placed on a firmer basis on their account. It is important to recall the fact, however, that cases of Pick's disease may lack gross atrophy whilst there are instances of Alzheimer's disease revealing themselves in so focal a way as to suggest the other. Both these disorders, and especially Alzheimer's dementia, may be diagnosed for certain by biopsy, and there is often justification for this measure, for it may also serve to establish or exclude the presence of other maladies. Angiography has been employed in the recognition of Pick's disease.

Certain Degenerative Conditions of the Brain associated with Dementia

Huntington's chorea.—In some reported instances the dementia, which may be regarded as an integral part of this disease, has preceded the choreiform movements, and occasionally the illness has run its course without any hyperkinesis, other afflicted members of the families showing the disease in a more typical form (Davenport and Muncey, 1916; Worster-Drought and Allen, 1929). Davenport and Muncey say " . . . there are among the children of typical choreics so many cases of dementia without choreic movements as to warrant the hypothesis that the dementing factor in a choreic strain may be inherited independently of the other symptoms." In a recent study of six cases, Stone and Falstein (1938) show that the atrophic process involves the brain as a whole and that the frontal and precentral parts especially are involved, particularly the ganglion cells of the third and fourth laminæ. As long ago as

1911, Alzheimer had stated that there could " hardly be a remaining doubt " that in Huntington's chorea severe degenerative processes were regularly present in the cerebral cortex. Dunlap (1927), in his classical paper on the subject, remarked that in pure and well-developed instances of the disease there were constant lesions present in the cerebral cortex as well as in the corpus striatum, but he admitted that to date he had been unable to convince himself that there was any true loss of cortical cells.

Minski and Guttmann (1938) remark that it does not seem possible to distinguish the dementia of Huntington's chorea from that in other types of dementing psychosis by any one specific feature such as a characteristic disturbance of thought. They note, however, that the most common mood seems to be one of indolence and apathy.

The so-called " Creutzfeldt-Jakob disease."—This condition was first described by Creutzfeldt in 1920 and later by Jakob in 1921. Some fourteen or more cases have so far been recorded which approximate to this disease, but there is still much uncertainty as to its entity. The changes are widespread and affect the basal ganglia and the deeper layers of the cerebral cortex, giving rise to partial degeneration of the pyramidal and extrapyramidal pathways. The disease, in its early stages, is said to be mistaken occasionally for disseminated sclerosis. The course varies from a few months to a couple of years, and the most usual age of onset has been in the fourth and fifth decades.

The symptomatology has been reviewed fully by Jansen and Monrad-Krohn (1937). There is a prodromal or " neurasthenic " stage of the illness which may last a few weeks or months. Slight alterations in temperament and memory may be noticed by the patient's friends, and complaint is made of weakness of the limbs, unsteadiness of gait, and insomnia. The malady develops in a subacute fashion into an " organic " stage in which neurological disturbances are widespread. There may be nystagmus, dysarthria, and ataxia. The limbs become spastic, with exaggeration of the deep reflexes and usually extensor plantar responses. Choreoathetoid movements may occur, but sensory changes are not evident, although complaint may be made of pains in the limbs. The psychical alterations represent a relentless march to a stage of profound dementia, and the earlier symptoms are no doubt determined by the patient's prepsychotic personality: thus there may be excitement, depression, or negativism. There is a tendency to confabulation, whilst delusions and hallucinations have been noted. Retentiveness is gradually lost and the intellect becomes blunted. Aphasia, epileptiform seizures, and loss of control of the sphincters gradually develop, and death takes place in a state of emaciation and complete dementia.

Yet at autopsy little unusual may be noted on naked eye examination of the brain. In the few cases that have been adequately described the histological appearances have been so variable that it is impossible to give a comprehensive account of them. There has been reported, however, an alteration in many of the nerve cells amounting to fatty degeneration, chromatolysis, or even complete disappearance, with a reactive hyperplasia and fibrous metamorphosis of the glia. The most affected parts are the frontal and temporal cortex, the subi-

culum and gyrus cinguli, while similar alterations may occur in the corpus striatum, the medial part of the optic thalamus, globus pallidus, substantia nigra, and cranial nerve nuclei. The parietal and occipital cortices appear to be largely spared. Some cases appear to have been predominantly cerebral rather than cerebrospinal.

There are three cases in the literature which Hallervorden (1930) has described as "atypical." The first was mentioned by von Economo and Schilder (1920), and it concerned a fifty-year-old-man who, following on a cold, developed pains and weakness in the legs. The illness lasted five years, and during the last five months of its course dysarthria, disorientation, dementia, and delirium supervened. The whole body became rigid and the face took on a Parkinson-like mask. Tendon reflexes were exaggerated and the plantar responses were extensor. Histologically, an increase of fat was found in the nerve cells of the cerebral cortex with some satellitosis but little cell atrophy. In the basal parts of the corpus striatum and substantia innominata there were symmetrically placed foci of glial overgrowth, together with a general proliferation of the glia. In the globus pallidus there was some cell atrophy, with reactive changes in the glia, and precipitates were found lying free, but there were no calcium deposits. In the cerebellum there was a fatty infiltration of the glial cells of the molecular layer and in the liver an interstitial hepatitis. This case is of considerable interest and it appears to be almost unique. In spite of the presence of hepatitis there is no resemblance either clinically or histologically to Wilson's disease. The second case was described by Fleischhacker (1924); the patient was a woman of forty, whose symptoms, in some respects, suggested paralysis agitans. There was a tremor of the upper limbs with transitory symptoms of a right-sided pyramidal lesion with spasm and paresis. Memory became impaired and she developed into a quarrelsome psychotic with ideas of persecution. The illness lasted twelve years. Histologically, there was found to be a diffuse nerve cell change of the whole brain, but especially in the large cells of the corpus striatum. The globus pallidus and substantia nigra were normal, but in the putamen there were extremely large glial cells with only a slight fibrillar metamorphosis. These cells were described by the author as being similar to Alzheimer's glial cells, only smaller. The third case was described by Gurewitsch (1921) ; it concerned a forty-three year-old man who developed severe mental alterations and neurological signs soon after an attack of pneumonia. At first the illness resembled Korsakov's syndrome, but the dementia later became profound and the cerebellar signs appear to have been considerable. At autopsy there were extensive degenerative changes in the nerve cells of moderate degree and an increase of cortical blia. There were some perivascular infiltrations in the cornu Ammonis, but these appear to have represented an isolated finding. There was hyperplasia of the glia in the corpus striatum and some degree of the same in the thalamus, red nucleus, and olives. The dentate nucleus was completely destroyed, but the cortex of the cerebellum and the cord were intact. A case not unlike this, but having some resemblance also to the group of parenchymatous cerebellar atrophies with mental changes, is to be reported elsewhere (McMenemey and

Pollak). Marinesco and Draganesco's case (1929) of a child of six years with the syndrome of Fœrster appears to resemble the Creutzfeldt-Jakob syndrome in many respects.

The first of Davison's (1932) cases falling into the so-called " Creutzfeldt-Jakob " group of diseases showed atrophy of the small muscles of the hands with corresponding changes in the anterior horn cells. In addition there are a few examples in the literature of " amyotrophic lateral sclerosis with dementia." That these are instances of the same order of disease seems very likely.

Nikitin (1925) described another variant of this disease, the clinical type being predominantly cerebellar. The characteristic feature in this case was the striking involvement of the white matter of the cord; he called it " sclerosis cerebello-pyramido-intercorticalis."

Davison suggests " disseminated encephalomyelopathy " as a good descriptive title for this disease to cover its underlying pathology, but until more is known about it he is in favour of retaining the title given to it by Jakob of " spastic pseudosclerosis." Wilson (1940) has shown this latter term to be both inaccurate and unsuitable. It would seem best to retain the names of Creutzfeldt and Jakob until more is known about this condition, and seeing that its real entity is in doubt to regard it as a syndrome rather than a disease. It remains at present a convenient dumping-ground for several instances of atypical presenile psychosis of unknown origin which run a rapid course and have for their histology a parenchymatous degeneration of the brain with some glial hyperplasia. Heidenhain's (1928) cases have been included in this group, but the early onset of amaurosis in the first two was more in keeping clinically, though not histologically, with Schilder's disease. Hallervorden (1930) and Jansen and Monrad-Krohn (1938) have both considered the possibility, in view of isolated examples wherein the cerebral vessels have shown occasional perivascular lymphocytic cuffing, of epidemic encephalitis in an unusual form; the likelihood cannot be seriously entertained. A more important question is the possible relationship of this disease to pellagra, with which it has certain histological features in common. In a high proportion of cases of the deficiency disease, however, there is collateral evidence in the form of a history of gastrointestinal upset or of the findings of skin lesions. It is uncertain whether cerebral forms of the disease may occur in the absence of more widespread symptoms and signs, but if so they would fall into line with the cerebral form of the Creutzfeldt-Jakob syndrome. The similarity, however, is sufficiently close to suggest an obvious line in treatment for such cases of psychosis, whilst the occasional reporting of amyotrophy warrants the simultaneous exhibition of vitamin E.

A familial incidence in this disease has so far been described only once: Meggendorfer and Stender (1930) report the case of a woman of forty-six whose brother, aged forty-four, was previously under the care of Kirschbaum (1924). With so few instances adequately described it would be illogical to be dogmatic as to the essential character of this syndrome, but one cannot but see a striking resemblance between it and Huntington's chorea, neither can one fail to see

that this condition forms a bridge between Huntington's chorea and the parenchymatous atrophies of the cerebellum, several of which are now known to be familial.

Primary Parenchymatous Cerebellar Atrophies

This group includes a series of presenile and senile instances of degenerative processes in the brain, the brunt of which falls on the highly organized cells of the cerebellum, the pons and the olives; it would appear, however, that other neurones may be involved, amongst them those of the cerebral cortex. The interrelation of these diseases is still far from clear, but a classification was suggested by Marie, Foix, and Alajounine (1922) which served for a time. Wilson (1940) adopted an anatomical classification, which is perhaps more satisfactory. The origin of the disease is attributed by Parker and Kernohan (1933) to a premature senescence of the Puakinje cells.

Coincident involvement of the cerebral cortex in this group of diseases has been mentioned by Fickler (1911), Schrœder and Kirschbaum (1928), Bogært (1928), Mathieu and Bertrand (1929), Bogært and Bertrand (1929), Guillain and Bertrand (1929), Akelaitis (1928), and Richter (1940). Thus it would seem that the subnormal intelligence which characterizes most instances of Freidreich's ataxia can be paralleled in those cerebellar atrophies occurring later in life. Akelaitis (1938) described a family in which there occurred in three generations five cases of primary parenchymatous atrophy of the cerebellar cortex in association with mental deterioration. He groups the hereditary and familial forms of cerebellar atrophy into, (*a*) olivopontocerebellar (ascending or cerebellopetal), and (*b*) primary parenchymatous (descending or cerebellofugal). The presence of these familial forms of the parenchymatous cerebellar atrophies at once serves to emphasize their abiotrophic nature and to bring them more into line with those familial degenerations of the cerebellum met with in younger persons. Mathieu and Bertrand (1929) emphasize the difficulty of differentiating between hypogenesis and progressive degeneration.

Wilson (1940) explains the psychical symptoms of primary parenchymatous cerebellar atrophy as being due to their toxic accompaniment: such would be, in part, an explanation of Greenfield's (1934) cases, but it would not account for all. Moreover, the atrophy of the Purkinje cells could equally well be explained on the basis of a toxæmia, for their instability is notorious and is probably far greater than that of the cells of the cerebral cortex. It is difficult to get away from the view that both the cells of the cerebral and cerebellar cortex are, in this disease, unusually susceptible to external influences, owing to an inherent lack of vitality.

There are two interesting cases in the literature which appear to be related to this group. The first was described by Claude, Lhermitte, and Baruk (1932). The patient was a man of fifty-seven, who, two years after an injury to the skull, began somewhat suddenly an illness which eventually showed itself as a profound emaciation, associated, paradoxically enough, with boulimia. The neurological disturbances amounted to a right-sided hypertonia, aphasia, and pseudobulbar signs, while the mental picture was dominated by negativism, a

lack of interest, disorientation, gesticulation, and turbulence, especially at night. Although the symptoms and signs would at first glance suggest an encephalitis, the histological findings showed no evidence of this: there was found an extensive nerve cell atrophy with secondary gliosis of the frontal cortex, lenticular and caudate nuclei, and the optic thalamus. The authors remark that only a formidable toxic agent could account for the lesions.

The other case was reported by Stern (1939) and it appears to be unique in the literature. The subject was a forty-year-old man who developed a severe dementia associated with iridoplegia, hypersomnia and forced grasping and sucking movements. The illness was of short duration. The histological analysis revealed a symmetrical degeneration of the nerve cells with consecutive gliosis of most of the optic thalamus and similar but less conspicuous changes in the cerebral cortex and inferior olives.

These diseases have all been included in the one group because they have this in common: they all reflect the importance of the constitutional factor in degenerative states of the central nervous system.

Dementia as a Symptom of Intracranial Tumour

Although a brain tumour seldom causes profound dementia, some degree of mental deterioration is not uncommon, and it may be the presenting, and for a time, the only symptom. In middle age the diagnosis of intracranial tumour may offer unusual difficulties: the early symptoms and signs may simulate those caused by cerebral arteriosclerosis or syphilis, and the occasional co-existence of a brain tumour with those conditions has to be borne in mind. Moreover, in a high percentage of cases, headache, vomiting and papillœdema may be absent (Hastings, 1939). A reason that has been suggested for this is that in the middle-aged and elderly, the subarachnoid space is more capacious than in younger subjects and a tumour can expand to a considerable size at the expense of this space before compensation is disturbed and symptoms of increased intracranial pressure result.

That the difficulties of diagnosis are very real is stressed by Hastings (1939) who found that at the Philadelphia General Hospital between 1928 and 1935, out of a total of one hundred and seventeen cases of intracranial tumour, there were twenty-five instances over the age of forty in which the correct diagnosis was established only at autopsy.

Is the Dementia a Primary or Secondary Symptom?

Symonds (1931) referred to the diagnostic importance of the mental changes which come before the onset of symptoms of increased intracranial pressure. The early alterations may be regarded as primary symptoms attributable to the nature and situation of the tumour, just as there may be paralysis, aphasia or defects in the visual fields before the secondary symptoms of increased intracranial pressure become manifest. It is, therefore, of prime importance to obtain a careful history, not only from the patient, but from his relatives and associates. The first signs and symptoms may appear so trivial to the

patient or his friends that their true importance is not realized. For this reason, the method of direct inquiry may have to be employed and attention directed specifically to any peculiarities of temperament or behaviour which may have been noticed, however slight or transient. To appreciate the full significance of these early symptoms, it is necessary to know as much as possible about the patient's " pre-psychotic personality " (Sachs, 1930).

Mental symptoms have been separated by Kinnier Wilson (1940) into two kinds, general and specific. The former, which can justly be described as negative rather than positive, amount to inattention, indifference, impaired memory and insight, and slowness of response. It is these symptoms of a general nature which are most commonly seen and they are more often due to the raised intracranial pressure than to the tumour itself. Alford (1937) goes so far as to stress the decisive value of these symptoms of a negative kind over more positive psychological findings in the study of the early intellectual defects of cerebral lesions. Intellectual disturbances are attributed by Kinnier Wilson (1931) to implication of the long association fibres, whereas emotional upset is usually found to be due to tumours near or within the ventricular system. According to Symonds (1931) mental deterioration is related to the total amount of white matter destroyed.

As a tumour grows, further symptoms appear and there may be signs of pressure upon important pathways in its vicinity. These symptoms may be due to involvement of the brain tissue by the tumour or to the general rise of intracranial pressure resulting from it, and they include dysarthria, apraxia, forced grasping movements, hemiparesis and epileptiform attacks. Papillœdema is said to be late if the tumour is situated anteriorly. The cerebrospinal fluid may show a rise in protein content, more especially if the neoplasm involves the basal surface of the brain (De Vet, 1936) or else has infiltrated to the cavity of a ventricle. Mental symptoms may be due not only to infiltration and destruction of brain parenchyma by the growth of local or general brain œdema, but may follow on a disturbance of the speech mechanism (Holmes, 1931) when the unhappy patient finds himself losing touch with his fellow men. They may also occur after impairment of cortical function other than that of speech control.

Dementia as a Guide in the Location of a Cerebral Tumour

When dementia is the presenting symptom, one's attention is naturally directed to the frontal region of the brain. But tumours situated in other localities may cause dementia, whilst it is within the experience of many that frontal neoplasms may occur without any disturbance of the intellect or emotions. The whole subject of mental symptoms associated with cerebral tumours was reviewed in a discussion at the Royal Society of Medicine in 1931. The general conclusion at that time was that the localizing value of mental symptoms was practically nil. Nevertheless, it is expedient to review the subject in the light of certain studies which have been recorded since that date.

Frontal.—Occasionally it happens that considerable portions of the frontal

lobes can be implicated with astonishingly slight disability. Such a case was described by Ackerly (1935). The patient was a woman whose right frontal lobe was removed on account of a midline meningioma which had caused severe compression also of the left frontal lobe. Two years afterwards there was said to be no significant diminution in intelligence or disturbance of emotion or general behaviour: the only symptom was a certain lack of distractibility. Rowe's (1937) patient, whose right cerebral hemisphere was removed on account of an astrocytoma, had as residual signs only a slight loss of inhibitions, some impairment of memory and a slightly disordered emotional tone. Dandy (1928) described five instances of removal of a whole hemisphere: in the three cases in which postoperative examinations were full there were found to be practically no mental symptoms. Brickner (1932), however, describes considerable alteration in personality and a loss of intellectual power after removal of both frontal lobes, and Rowe (1937) concludes that the higher cerebral functions of man are more severely altered by bilateral frontal lobe lesions than by corresponding or even more extensive lesions of any other area, an opinion which would appear to be substantiated by the findings of others. Thus Frazier (1936), in a review of 105 cases of frontal lobe tumour, draws attention to the importance of a bilateral involvement of the brain for the development of mental symptoms. Moreover, Duus (1939) has analysed the psychic disturbances accompanying tumours of the orbital part of the frontal lobe and from a study of five cases of his own and twenty-five in the literature he concludes that they are usually due to bilateral meningiomas occurring in middle-aged persons. He noted that character changes developed consistently early, whilst the more general signs of raised intracranial pressure came later. Schrœder (1939), however, after presenting eighteen new cases of frontal lobe tumours observed that the symptoms depended more on the accompanying œdema than on the actual involvement of the brain. Mental symptoms are usual, he says, because the white matter is so often involved in the œdema, which serves to obstruct the blood flow, thus impairing nutrition and function.

Thus it would appear from these various observations that it is the bilaterality of frontal cortex involvement which is of prime importance for the development of mental symptoms. Worster-Drought (1931) states that a left frontal lobe lesion, in his experience, is more liable to give rise to disorder of conduct and even dementia than a lesion of the right frontal lobe, the latter being more likely to be associated with amnesia and confusion.

The more recent psychological studies in frontal lobe lesions such as those of Goldstein and Katz (1937) have shown that a great deal is to be learnt by a careful analysis of the mental symptoms, adding that "it appears justifiable to make a diagnosis of a lesion of the frontal lobes on the basis of mental changes." The studies of Penfield and Evans (1935), too, show the importance which must be attached to a thorough knowledge of the patient before symptoms of a negative character can be fully evaluated.

Temporal.—Golla (1931), in a series of fifty-five cases of intracranial tumour causing mental symptoms collected from the Claybury and Maudsley hospitals,

found that nineteen of them were situated in the temporal whereas only eleven were in the frontal lobe: the majority of them were in the right temporal region. Collier (1929) remarked that the most dramatic mental changes that he had seen attributable to a brain tumour had been in instances of neoplasms in the temporal lobe, the outer surface of the occipital cortex and the splenium of the corpus callosum respectively.

Corpus callosum.—Involvement of the corpus callosum by neoplasms may give rise to mental disturbance, but some degree of apraxia and hemiparesis is usually present to give a clue to the locality of the lesion. Ironside and Guttmacher (1929) remark on the similarity of the symptomatology to that of cerebral arteriosclerosis, especially when psychical changes co-exist with bilateral pyramidal signs and tremor or other involuntary movements. It is interesting to note that the apparent ataxia which characterizes some of these cases is attributed by Barre (1939) to an impairment of attention. Craner (1936) described six cases of tumour involving the corpus callosum. It would appear from his observations that growths involving the splenium may cause symptoms of progressive loss of memory for recent events, an appearance of mental confusion, disorientation and unsteadiness of gait. In the two examples in which only the splenium of the corpus callosum was involved headaches were absent and papillœdema was questionable in one (case 6) and had subsided in the other (case 5). In the latter case symptoms had been present for eight years. Although it would be rash to attribute too much importance to so small a series it is worthy of note that those two cases which presented themselves as early instances of dementia tended to lack the classical triad of brain tumour symptoms.

Third ventricle.—Riddoch (1936) reported two instances of tumours of the third ventricle, one of them a colloid cyst, giving rise to dementia in the absence of headache and changes in the fundus oculi. Nielson and Raney (1940) stress the importance of alteration in effect and personality, and also amnesia for recent events, in establishing the presence of tumours in the region of the third ventricle.

Basal ganglia.—Smyth and Stern (1938) have commented upon dementia as a finding in certain cases of tumour involving the optic thalamus. In four out of six instances mental symptoms occurred early and in two of them dementia was the most outstanding sign: in these two cases there was bilateral involvement of the medial thalamic nuclei and the authors make a tentative suggestion that this may be an important factor in determining the appearance of dementia.

Posterior fossa.—Brain (1931) commented on the profound mental disturbances which may be associated with tumours of the posterior fossa.

Mental hospital cases.—Cerebral tumours rarely present mental symptoms sufficient to justify admission to a mental hospital. Figures were quoted by Golla in 1931. An analysis of material collected from 1,320 consecutive autopsies performed at Napsbury Hospital showed only twenty instances of intracranial tumour representing 0·41 per cent. of admissions: in only nine of these (0·205 per cent.) were the symptoms responsible for their admission to

hospital. The presenting symptom, too, was nearly always mental confusion which tended to obscure any dementia which may have developed. Perhaps metastatic neoplasms are the commonest tumours to cause mental confusion, and foremost amongst them must be listed the bronchial carcinoma. Occasionally, a growth may spread diffusely over the meninges: an example wherein a woman of fifty-eight had symptoms of ingravescent dementia for five months prior to the onset of more general symptoms of raised intracranial pressure was referred to by Greenfield (1938), who aptly points out how readily such a condition of the meninges may be overlooked at autopsy.

Conclusion

Out of all that has been written about mental symptoms in intracranial tumours, the one fact which emerges clearly is that we have yet much to learn about them. The localizing value of these symptoms is of great psychophysiological interest, but for purposes of diagnosis more exact methods, such as ventriculography, have to be employed.

Aneurysm and Trauma as Causes of Dementia

Intracranial aneurysm.—As the possibility of an intracranial aneurysm must be entertained in the differential diagnosis of a cerebral tumour, brief mention will be made of it here. If an aneurysm arises from the anterior communicating or from one of the anterior cerebral arteries and attains any degree of size, it may cause considerable distortion of the frontal lobes and interfere with their nutrition with consequent development of mental symptoms. But dementia, without localizing signs, is unusual and headache is a very frequent symptom. Moreover, a history of one or more acute phases of the illness corresponding to periods of rapid distention of the aneurysmal sac can often be elicited. It should be emphasized again that by no means all patients with frontal lobe lesions, be they tumour or aneurysms, develop mental symptoms ; there would appear to be some inherent and predisposing factor which determines this. Kinnier Wilson (1940) has said that the mental symptoms may spring from the soil as a purely indirect sequel of the growth. Aneurysms are found at autopsy at all ages, but they seldom give rise to symptoms before the age of twenty. Not a few of them are symptomless until the advent of middle age when the vascular system becomes less elastic and when the blood pressure may begin to rise.

Trauma.—A few cases of progressive dementia are accounted for, either by a chronic subdural hæmatoma, or, less frequently, by cerebral concussion giving rise to subsequent diffuse glial scars. The former occurs most commonly over the parietal region and one-third of the cases are bilateral. The symptoms and signs may resemble closely those of a cerebral tumour so that it becomes of prime importance to inquire not only for a history of trauma but for accurate particulars of the mental state of the patient immediately following the accident. In this connection one recalls the frequency with which persons

with cerebral tumours recollect blows on the head which they are quick to associate with their symptoms; although there is some evidence to show that there is an association between them, more often than not the occurrence is fortuitous. But the blow is seldom as severe as is usually encountered in instances of subdural hæmatoma. Nevertheless, these latter patients occasionally find their way into mental hpspitals without any clear history of trauma, whilst alcoholics frequently subject themselves to trauma but often fail to recollect any such event. A history of alcoholism and the possibility of other toxic agents will be reviewed during the anamnesis, but such diseases, as well as syphilis and other disorders which are general and are not just confined to the brain, will be readily recognized in a general examination of the patient because of the collateral manifestations.

The so-called " post-concussional syndrome " gives a history of severe headaches made worse on moving the head. The more striking symptoms are attacks of giddiness with vomiting, but of greater interest are the neurasthenic tendencies which develop later with irritability and sometimes more distressing alterations of personality. Ultimately symptoms of dementia may ensue with gradual deterioration of memory and intellect, slovenliness and melancholia. This interesting disorder has for its histological basis a neuronal degeneration of the cerebral cortex attributable in part to the sudden vascular alterations caused at the time of the injury. It is not often that the dementia is severe and usually the patient is only too ready to relate the circumstances of the injury.

Syphilis as a Cause of Dementia

It is unnecessary to refer to so well recognized a cause of dementia as general paralysis except to stress the fact that the blood Wassermann reaction may, in cases wherein syphilis was contracted many years previously, be reported sometimes as negative even in the absence of a history of antisyphilitic treatment. This impression is confirmed by Petersen (1937) who found a negative Wassermann reaction in the blood in as high a proportion as 11·6 per cent. of cases. This is contrary to what is stated in many of the textbooks which maintain that the blood Wassermann is positive in 100 per cent. of instances. The employment, however, of a sensitive Wassermann technique when congenital, oldstanding or treated lues is expected will usually detect all general paretics, but the Wassermann tests in general use, which are designed rather to assist in the recognition of cases requiring antisyphilitic treatment, may miss these weak positive reactors. Thus it is not unusual to find patients admitted to hospital with the story of having had a negative blood test outside, yet subsequent examination has shown their blood to be weakly positive with a sensitive technique. In the laboratory diagnosis of neurosyphilis it is desirable to make use of one or more of the flocculation tests as auxiliaries. The Meinicke and Müller reactions, for instance, have proved themselves invaluable for the recognition of oldstanding and treated cases. But, if an examination of the blood proves unhelpful, the cerebrospinal fluid will nearly always reveal the true state of affairs, authentic instances of untreated general paralysis not

showing changes being distinctly rare. Here again the employment of a flocculation test is helpful: in particular the Müller reaction would seem to offer valuable confirmation of old-established disease. It is a wise practice always to collect both blood and fluid at the same time from any case in which general paresis has to be excluded. This provides against the possibility of this disease being missed simply because the blood Wassermann happens to be negative. This is of particular importance in mental hospital practice where many of the patients may have received sufficient antisyphilitic treatment to render the blood Wassermann negative before the advent of mental symptoms. The importance of a thorough serological investigation must be stressed because not a few instances of naturally or therapeutically arrested general paresis have, in the past, been described as examples of idiopathic presenile dementia, the clinical and histological features being atypical of the former. General paresis should be diagnosed at the stage when mental symptoms are appearing and before the advent of physical signs in the central nervous system. " Stationary" paralysis may give rise to difficulty in diagnosis, for the smouldering nature of the disease may be reflected in indefinite serological findings. Galbraith (1940), however, has reported a case, having diagnostic serological confirmation, which was stationary for thirty-one years, only one year less than the classical example described by Gaupp and Alzheimer (1907). Examination of the blood and cerebrospinal fluid plays therefore an essential part in establishing the diagnosis, and it is in order to avoid missing this disease in its early, and especially its atypical, forms that one must employ them as a routine examination in any case of dementia.

Short of general paralysis dementia may occur in other varieties of neurosyphilis and particular mention should be made of syphilis of the cerebral blood vessels. If this disease is allowed to establish itself one or more thromboses may occur as the result of an obliterative endarteritis with infarction of the brain of greater or less degree depending upon the size and location of the obstructed vessel. When the thrombotic areas are found scattered throughout the white matter of the cerebral hemispheres, as sometimes happens, and particularly when the softened areas are placed anteriorly, it is little wonder that dementia ensues. Histological examination of such a brain reveals a well ordered reparative activity on the part of the mesoglia and a relative lack of any degree of active syphilitic inflammation. For these reasons, if the disease is taken early, the prognosis is hopeful and the patient may obtain many years of useful life.

Arteriosclerosis and Dementia

Under the heading of " arteriosclerlosis " there is a bewildering variety of conditions which have their origin in an impoverishment of the blood supply to the brain due to disease of the blood vessels. Arteriosclerosis is not a disease (Allbutt, 1915) but a pathological process. Evans (1923) has likened the term " arteriosclerosis " to a crêche for children who have not known their

parents or who have so little individuality that they cannot be distinguished apart.

It is not proposed to do more than outline the varieties of cerebral arteriosclerosis, but reference will be made first to certain difficulties met with in the recognition of this disease.

In the first place, arterial disease may be strictly local in its incidence in the body, so that it is difficult to deny the possibility of cerebral arteriosclerosis in a person who has passed the fortieth year, even if the cardiovascular system, as a whole, is above reproach. Neuberger (quoted by Biggart, 1936), studying this dissociation, found arteriosclerosis of the peripheral vessels in only 10 per cent. of cases of cerebral vascular disease. Even the retinal arteries may be spared when the intracranial vessels are actively involved: and the converse is true, for one cannot be certain that the cerebral vessels are diseased even if the retinal or radial arteries are tortuous. This patchy distribution of arteriosclerosis often gives rise to faulty diagnosis. On the other hand, the relationship between changes in the vessels of the brain and kidneys is more intimate than that which obtains between the cerebral and peripheral vessels: in old age they often appear to react almost identically so that there would seem to be a common cause for their behaviour. It has been said that the reason for the erratic incidence of arterial disease lies in the factor of local strain. But this explanation should not close one's eyes to other possibilities, such, for instance, as the likelihood of sepsis in the near locality contributing to the disease. In this connection it has been suggested that chronic ethmoidal and sphenoidal sinusitis may play some part in the ætiology of sclerosis of the vessels constituting the circle of Willis, but the evidence has not been convincing. The important fact, however, which emerges from collected experience is that cerebral arteriosclerosis may be unaccompanied by general arteriosclerosis. But not only may arterial disease be localized to the brain, it may be confined to one part of the brain: perhaps the most striking instance of this is that variety of arteriosclerosis described first by Binswanger (1895), and more recently by Farnell and Globus (1932), affecting the subcortical arterioles and giving rise to a symptomatology and histological picture which bears some resemblance to Schilder's disease.

Secondly, we are, at present, not skilled in recognizing the earliest stages of arterial disease. It requires a microscope to recognize thickening and proliferation of a capillary vessel, but preceding the structural changes in the capillaries there must be alterations in function which we are unable to detect, for we have no means, as yet, of examining in a critical way the capillary bed of the brain during life. The importance of functional vascular disturbances cannot be overrated, for this conception has dominated recent work on cerebral arteriosclerosis and hæmorrhage (Stern, 1938). One concludes, therefore, that it is almost impossible to say whether cerebralvascular changes have begun in any given case or not. Moreover, even a vessel with advanced disease may still be able to function without apparent detriment to the parenchyma which it subserves.

Lastly, one must reckon with the fact that senescence is entitled to a certain

amount of vascular change and it is sometimes difficult to decide if this allowance has been exceeded. These changes have been described by Baker (1937). Senescence is not to be regarded as a disease: neither must the involutional processes accompanying it be regarded as pathological events, but senescence occurring before its time is abnormal. And here perhaps is some justification for retaining the terms " presenium " and " senium " in our nomenclature: for after the age of sixty, we expect to find some vascular alteration, but before this age we are justified in regarding such changes as pathological.

The occurrence of arterial changes secondary to already existing disease requires only to be mentioned because of the possibility of its being mistaken for primary vascular disease. There are many examples of this in neuropathology, particularly in the degenerative disorders, where we find vessels removing products of catabolism and becoming themselves diseased as a result of the local stasis and accumulation of lipoids.

Finally, a not infrequent histological anomaly is the presence of a much diseased vessel and an apparently healthy area of irrigation; or one may find pathological reactions around perfectly healthy looking vessels. When faced with these problems one must recall the anastomotic pattern of the cerebral vessels and the fact that not all transudates from vessels can be expected to show themselves in histological preparations.

The histological variants of cerebral arteriosclerosis short of encephalomalacia are catalogued by Hassin (1933) as follows: (1) Alzheimer's senile cortical sclerosis ; (2) perivascular gliosis; (3) Binswanger's " chronic subcortical encephalitis "; (4) Pierre Marie's état lacunaire, and Grasset's progressive lacunar cerebrosclerosis; (5) état criblé (Durand-Fardel); (6) état vermoulu (pierre Marie); (7) verrucose atrophy (Spatz); and (8) schizogyria (Mittlebach and Spatz). Some of these conditions, however, are only to be expected in the senile decades. Greenfield's classification (1938) of the forms of presenile dementia associated with vascular disease is simple and adequate. In his first category, the one most frequently met with, he places all examples with softenings or hæmorrhage, adding that little is to be gained by giving different names to forms in which the predominant change is of one or other character. He mentions, however, a rare variant met with in subjects of hyperpiesis in which multiple slit-like hæmorrhages are found chiefly in the subcortical white matter. He suggests that the pathogenesis of this form of the disease, as well as Binswanger's encephalopathy, may be related to the relative absence of anastomoses in the long vascular branches going to this part of the white matter. For his second type he recognizes the verrucose or granular atrophy of the cortex which is usually found in association with renal arteriosclerosis and hyperpiesis. This condition, which affects in an irregular manner both the nerve cells and fibres in the cortex and is associated with an overgrowth of neuroglial fibres, depends upon sclerosis of the small cortical arterioles and is presumably identical with the disease known as diffuse hyperplastic sclerosis (Evans, 1921) and arteriocapillary fibrosis (Gull and Sutton, 1872). These latter authors described the changes in the pia mater, whilst Evans paid special attention to the arterioles of the medulla and midbrain.

The third form of progressive vascular disease, often associated in life with hypertension, is that in which no naked-eye changes are present either in the vessels or in the texture of the brain apart from indefinite thinning of the gyri. There is proliferation of the intima in the small cortical vessels together with numerous and widely scattered areas of focal degeneration or rarefaction (" lichtung ") of the nerve cells. The glial alterations are minimal. Greenfield regards this form of cortical disease as closely allied to the changes described in Kræpelin's presenile psychosis, and also to those found in epileptics associated with mental deterioration.

Cerebral arteriopathy, in one of its many forms, contributes a fair proportion of the cases of dementia in the presenile group. Hypertension may be absent (Grünthal, 1935). In general, the progressive mental deterioration is associated with focal signs which have their origin in the disseminated lesions which we have referred to. The two most helpful points in the clinical recognition of the disease would appear to be the retention of insight until late on in the illness and the frequent occurrence of fluctuations and remissions in the course of the disease. Neurological signs are common, especially if one or more of the vessels has become occluded. Mental changes with apraxia are said to develop in the absence of any paralysis, however, if the callosal branches of the anterior cerebral arteries are occluded alone. An increase in the protein content of the cerebrospinal fluid may occur, especially if there is some complication such as cerebral thrombosis, uræmia or congestive heart failure. However, this increase of protein seems less likely in cerebral arteriosclerosis than in intracranial tumour. In Merritt and Fremont-Smith's studies (1937) only 25 per cent. of the former had a protein content over 45 mgms. per cent. whereas the corresponding percentage for cerebral tumour was 69.

Miscellaneous Conditions which may cause Presenile Dementia

There remain several diseases which may give rise to a picture of presenile dementia.

Schilder's disease.—Although at first thought to be essentially a disease of childhood, it is now known that it may be met with later in life. In Bouman's series of one hundred cases of diffuse sclerosis, eleven were over the age of forty.

The essence of the pathology is a gradual dissolution of the periaxial white matter with a resulting gliosis. Sometimes familial, many different histological varieties of it are seen suggesting all stages between a frankly infective and a mildly degenerative process. No doubt it has more than one cause and the ætiological factors, which, as MacNamara and Dickson (1932) and Meyer and Pilkington (1936) have suggested, may be extracerebral, may differ in two cases which histologically are identical. Bogært and Dewulf (1939) have described an example of seventeen years' duration following on a fall. Meyer and Tennent (1936) suggest the possibility of avitaminosis as a cause. Globus (1932) comments on the frequency of a gastrointestinal onset, while Winkleman and Moore (1939) describe a case with sudden onset at the

age of thirty-seven ushered in by an infection of the upper respiratory tract. These last authors speak of the need for a search for " a common denominator." The classical type of Schilder described in children frequently had a symmetrical spread of the lesion from the occipital poles anteriorly. Amaurosis of central origin was therefore to be expected. But in older subjects this need not necessarily be the case and the first symptom may be referable to the frontal lobes (Ferraro, 1937). Undoubtedly, Schilder's disease to date has included other conditions which, in the course of time will be separated off from the parent group, but as we know it at present it is not always symmetrical in its progress, neither is it invariably progressive, certain examples of apparent arrest being known. It has been said that Schilder's disease must be reckoned with in the differential diagnosis of any case presenting evidence of a progressively destructive lesion of the brain, so that it must be considered as a possible, although a rare cause, of presenile dementia. With regard to nomenclature it would seem desirable to retain the term Schilder's disease for this group of maladies for the time being. " Diffuse sclerosis " is a less desirable title because it stresses that histological feature which is surely of secondary occurrence and importance. " Encephalitis periaxialis diffusa " is a convenient pathological name provided one is prepared to regard the inflammatory process in its broader sense as suggested by Aschoff to include reparative and regenerative phenomena as well as the frankly infective.

Marchiafava-Bignami disease.—Dementia is a symptom of this remarkable disease, the essence of which is a demyelination of the corpus callosum. Other parts of the white matter may be affected as, for instance, the anterior commissure, the brachium pontis, the subcortical white matter or even the optic chiasma. According to King and Meehan (1936), the process is related in some way as yet unknown to the vascular system. The first three cases were described together as a clinical entity by Marchiafava and Bignami in 1903. Since then some forty examples have been described, but they have all been Italian men. The first case to be reported from America (King and Meehan) was an Italian. It is possible now that the disease is becoming better known that more cases will be recognized and that it will be found not to be confined to the Italian race: on the other hand, we may have, in this disease, a true example of a racial constitutional weakness manifesting itself when precipitating external influences are brought to bear on it. An alcoholic history or a family history seems to be usual. King and Meehan summarize the clinical findings as follows: emotional disorders, exaggerated excitability and irrascibility or else apathy, moral perversions and sexual misdemeanours leading to intellectual decay and dementia sometimes with confusion. Fits may occur and tremors, dysarthria, transitory hemiparesis and paraparesis are common. There is much wasting in the late stages of the illness, the duration of which is given as from three to six years with a tendency to remissions.

" *Toxic encephalopathies.*"—Mental deterioration, sometimes of considerable degree, may be associated with certain known toxic factors. Whether these toxic agents, and they include alcohol, lead and uræmia, are primarily the cause of the dementia or whether they are precipitating factors in constitu-

tions mentally unstable is not known. The latter alternative would seem to be the more likely, but it has been suggested that other factors, such as secondary avitaminosis consequent upon chronic atrophic gastritis may play some part.

An atrophy of the brain attributable to alcoholism in a presenile person is unusual, but some degree of cell change is common; its amount, however, seems to bear little relationship to the clinical symptoms. Morel (1939) has described a degeneration of the third layer of the frontal cortex in alcoholic psychotics.

The diagnosis of these cases is usually aided by the findings of some signs of peripheral neuritis. Alcoholism sometimes presents itself in the form of a pseudoparesis with dementia ; but alcoholism and general paresis may and do frequently coexist, and this fact has been advanced as the probable reason for the better prognosis in cases of general paresis of the exalted type as compared with those of the melancholic variety, for the former tend to show a greater addiction to alcohol, so that with institutional treatment a greater amelioration in their symptoms is to be expected.

Other diseases may cause regression of the mind in middle-aged persons, but they have been excluded from this study because the dementia, when present, occurs late on, and is not the most prominent symptom. For this reason epilepsy, disseminated sclerosis and epidemic encephalitis have been omitted. Marchand, Demay, and Naudascher (1938) have described the case of a woman of fifty-seven who developed an agitated melancholia. Death occurred two years later after a short attack of bronchopneumonia. At autopsy they found a tuberculous meningitis and two tuberculomas which were thought to have contributed towards the state of presenile dementia.

There remain two diseases—presbyophrenia and " simple " presenile dementia—which have been hinted at by several observers but about the pathology of which there is still doubt. Whether they are the same entity or both stages in the development of Alzheimer's disease or even cerebral arteriopathy remains to be seen. The terms would appear to be convenient in a clinical classification, but at present their pathological individuality is uncertain. Fischer (1910) recognized a presbyophrenic dementia as distinct from Alzheimer's disease on pathological grounds, but Henderson and Maclachlan (1930) regard them as different stages in the same process. A true decortication would seem to occur also in some instances which clinically fall into the groups of involutional melancholia and the late form of schizophrenia, but there is the possibility that they may be mixed cases. There would, however, seem to be some theoretical reason for recognizing a " simple " presenile dementia wherein the atrophy, unlike Pick's disease, would be generalized and not confined to one or more parts of the brain. Such a condition would serve as a link between Pick's disease and the Creutzfeld-Jakob syndrome.

The Rôle of Abiotrophy

The term " abiotrophy " was first employed in 1902 by Sir William Gowers at a lecture delivered at the National Hospital. Choosing for his text the

familiar example of baldness, he propounded the theory of limited vitality of organs and referred to certain nervous disorders wherein a particular system manifested a weakness throughout a family. This conception of abiotrophic diseases had been mentioned three years previously at a meeting of the Pathological Society of London when he replied to an address delivered by Dr. F. W. Mott on the pathology of tabes dorsalis and general paralysis. Dr. Mott had asked whether the toxic agent did not lower the durability of the nerve elements so that some other factor induced a premature decay. Sir William Gowers replied that he "had long felt that this disposition to decay, sometimes inherent, strongly or slightly, seemed to be induced artificially by toxic and perhaps other influences." In his Croonian lectures for 1900, Mott referred to the inherent vitality of the neurone as being the determining internal cause of disease of the central nervous system. The conception, however, was not new. Thus Powell, in Quain's " Dictionary of Medicine," 1883, referred to a group of diathetic diseases which " are of the nature of premature senility, attacking certain tissues or organs . . . from some inherent defect in their vitality," whilst in 1855, Walshe talked of "diseases apparently generated and sustained by an intrinsic blood poison resulting from some perversion of the nutritive processes of the individual." In 1830, we find Forbes Winslow quoting Gooch as having said that many of the diseases commonly attributed to cerebral congestion arise from a deficiency of nervous power and require for their removal " not depletion but support." Going back farther, we find the importance of the intrinsic factor in disease stressed by many writers: thus Cheyne (1725) remarks " the Failure may be in the Patient himself " and again " some chronical Distempers are such . . . by being Hereditary and interwoven with the Principles of Life, as never to be totally overcome," whilst Cooke (1685) says that " the Causes of diseases may be remote, between which and the Disease comes another Cause which is not in all diseases: this latter is either internal (called the Antecedent) consisting in the humours which have their being in the Body, which though at present they act not yet they may generate a disease." Finally, Aristotle had talked of " a lack of the inborn capacity of easy resistance to unhealthy influences " (Garrod 1927).

The term " abiotrophy " has served as a useful cloak for ignorance, and, for this reason, has, at one time or another, come in for a certain amount of disfavour : nevertheless, every year brings to light additional instances of familial disorders of the central nervous system, each of which serves to strengthen the argument for the recognition of abiotrophy. The majority of the diseases referred to above have familial instances, i.e. Pick's disease, Alzheimer's disease, Huntington's chorea, Schilder's disease, the Creutzfeldt-Jakob syndrome, the cerebellar atrophies and even cerebral arteriosclerosis, whilst the remarkable racial incidence of the Marchiafava-Bignami disease is suggestive of the same constitutional trend. Abiotrophy, however, does not preclude further analysis and it should not be regarded as a teleological entity; for this reason, one must not despair of attempting treatment. According to Myerson (1939), constitution is profoundly influenced by environmental agents and many conditions which we at present rightly regard as hereditary had better

be classed as constitutional. Myerson says " we may be chary of ascribing to heredity, dysfunction or lowered capacity when environmental circumstances are such as to favour the appearance of abnormality and inferiority and are unfavourable to full development. It is probable that we must look more to the earliest and earlier environments of man for the explanation of defect and aberration than to the later environmental situations, although they, too, have their place in the sun as explanatory of malfunction." An abiotrophic disease may, therefore, be conditioned by the lack of, or unavailability of, some ferment, vitamin or hormone which might conceivably be supplied therapeutically. In the realm of nosology, there are often the two factors, the endogenous and the exogenous : the former may be described as the abiotrophic tendency and the stronger this propensity is, the less will the exogenous factor need to be to precipitate the illness. Garrod (1927) says " in the abiotrophies the tissue defects are the most potent causative factors and the influence of external exciting causes is minimal." Rosenbach suggested that the vitality of the concerned tissues might be so low that even normal function overtries it. This view is paralleled by that of Critchley (1939), who refers to the possibility of involutional changes being localized to certain neuronic systems and appearing therein at an exceptionally early age. The exogenous factor, therefore, is often thought to be minimal and may be of the nature of a " subinfection " (Adami, 1914). Meyer and Cook (1937), however, note the frequency of pathological processes accompanying developmental lesions and they believe the extrinsic factor to be often of import. They say " more often than is realized, developmental arrest is only the indicator of the time of the damage and not the expression of an intrinsic, abiotrophic or faulty tendency of the tissue." The so-called extrinsic factor referred to by these authors, however, may, in point of fact, be intrinsic, for the gliosis which they regard as an index of bodily response to the extrinsic agent may have been determined by a biochemical aberration which can be regarded as an intrinsic dysfunction, although, it in turn, might be instigated by either an intrinsic or an external predisposing factor.

The concept of abiotrophy or tissue defect, therefore, is seen to imply more than an hereditary disposition, for it presupposes the constitutional factor which is dependent upon environmental influences. The importance of external agencies may, at times, be questionable, but it can be said in general, that it varies inversely with the inherent weakness of the tissue concerned.

The Limitations of Histology

The first classification of disease was, of necessity, based entirely upon clinical findings. In the nineteenth century, however, histology came to the aid of medical philosophy and a more accurate ordering of disease was possible. Yet in 1848 we find Graves warning us against " the fine-drawn and ill-founded observations of those who profess to account for every nervous disturbance during life by cerebral lesions." But morbid histology still furnishes the most

useful means of classification although it cannot be regarded as ideal. It has many drawbacks. Savage (1899) said, on this very topic, " the debris in a wrecked house is the same whether the fire originated in lightning or a paraffin lamp." Histology reveals but a sight of the battlefield when the engagement is over, but even here some idea of the varying fortunes of the fight can be gained by a critical analysis of the evidence before one's eyes. The senile plaques are not in themselves a cause of dementia, but they are the outward and visible signs of the struggle between the host and the pathogenic agent which induced the symptoms of dementia. The same applies to the neurofibrils when they have adopted the bizarre cadaveric positions so characteristic of Alzheimer's disease. Moreover, there is no quantitative relationship between clinical and pathological changes in this disease and in senile dementia (Rothschild 1937). But in the realm of neuropsychiatry there are many functional and probably also biochemical abnormalities which cannot be made to reveal their presence by means of the fixatives and impregnations at our disposal. Pursuing the above analogy one might say that there may be little evidence on the ground of the serious aerial combat which has taken place some hours before overhead. As our techniques become more perfect, further histological revelations throw additional light on our knowledge of disease. The methods of impregnation with silver and gold and the benzidine-nitroprusside technique of Pickworth (1934) constituted distinct advances in the histological approach, and now we watch with interest the more recent attempts at histochemical analysis.

At present, the need is for a more critical study of those diseases of the brain which one might describe as histologically non-spectacular. They constitute the majority of the diseases of the mind. Histology, in this particular field, has, in the past, been disappointing, but more might be learnt from it then has been the case to date. Yet histology alone will not contribute all; the diseases must be studied from every possible approach.

Conclusion

It is to be hoped that researchers will devote more time to an exhaustive study of the interesting group of dementias met with in middle age. The histologist should receive every encouragement to examine material from such cases and good clinical data should be amassed for the benefit of subsequent workers in this field. More instances of familial diseases might be disclosed if more exhaustive family and environmental histories were taken : for the smaller the family the less chance is there of a familial disease manifesting itself as such. At present there is much confusion in this group of diseases, for the number of atypical cases which do not readily fit into any group is considerable. Nevertheless, the unitarians are in the ascendancy. We find von Braunmühl (1932) advocating that Pick's disease, Alzheimer's disease, and senile dementia, and perhaps other degenerative diseases as well, are varying

aspects of the same general type of tissue reaction to disease. Jonesco-Sisesti and Strœsco (1939) argue on similar lines.

Having their origin at a time of life when physical and mental stress are often at their highest and when involutional processes are beginning, the presenile dementias may hold many secrets concerning the ætiology of organic disease of the nervous system, and they may be instrumental in clarifying our views on the much-debated problems of diathesis and abiotrophy.

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Dermoid Tumour in the Foramen Magnum, with Astereognosis and Dissociated Sensory Loss. E. A. Weinstein and I. S. Wechsler. 162.

Tumours of Cervical Spinal Cord.—In a study of 91 surgically verified cases of tumour of the cervical region of the spinal cord it has been found that pain in the neck is the outstanding early symptom. Muscular weakness usually begins in the arms but may involve the legs, is progressive and is usually the patient's chief complaint. Dissociation of a sensory disturbance is a constant accompaniment of all types of lesions of the cervical portion of the cord, but is not in itself diagnostic of any one type of condition. Lumbar puncture with careful manometric studies and complete examination of the cerebrospinal fluid are of great diagnostic value. Abnormal findings in one or both tests are almost constantly associated with neoplasms that involve the cervical portion of the spinal cord. Sphincteric disturbances of variable degrees were present in many cases, but were not of diagnostic or localizing value. Surgical management of tumours of the spinal cord consists of hemilaminectomy on the side of the tumour. This gives adequate exposure without sacrificing the stability of the vertebral column. (R. M. S.)

Landry's Paralysis.—In at least 30 per cent. of cases of acute ascending paralysis there is no clue as to the cause, either in the pathological study of the nervous system and other organs of the body or in the clinical features. In many cases the paralysis appears to follow closely on the heels of an infection and in a small number of cases, in which no pathological lesions may be demonstrated, the cause is accurately known. The best example of this type is "tic" paralysis. Acute ascending paralysis may also be caused by the sting of a weaver fish, vaccine therapy or antitetanus inoculation, or it may be associated with hæmatoporphyrinuria and with pregnancy. The disease may occur in association with pathological processes elsewhere in the body. Among these are typhoid fever, herpes zoster, lymphogranuloma, malaria, leukæmia, rabies, and antirabic vaccine. The pathological background in cases of acute ascending paralysis has always been elusive and it has been a constant surprise to find cases in which there were profound objective neurological changes and few or no evidences of damage in the nervous system. The great variability in the findings suggest, first, that included under the acute ascending paralysis of Landry are many types of the disease for which there are different causes, and, second, that, as for example in botulism, the primary damage may not necessarily be within the nervous system. (R. M. S.)

Dural Headache.—The authors point out that not all headaches are produced by the same structural mechanism or subserved by the same nerve pathways. Most headaches appear to be dural in origin, using this term to include the sinuses and veins tributary to the sinuses in their course across the sub-arachnoid space. Other sources of headache which have been suggested are the cerebral arteries and the walls of the third and lateral ventricles of the brain. (R. M. S.)

Recklinghausen's Disease.—A report dealing with a family in which Recklinghausen's disease, in the form of bilateral acoustic tumours, had been transmitted as a dominant mendelian trait through six generations. (R. M. S.)

Innervation of Annulus Fibrosus.—The annulus fibrosus and the posterior longitudinal ligament between the fourth and the fifth lumbar vertebra are innervated by fine unmyelinated nerve fibres. Their exact origin and course were not determined. The fibres end in naked nerve endings in the annulus fibrosus, and in like manner in the posterior longitudinal ligament with glomerulus-like terminations as well. (R. M. S.)

Jacksonian Seizures.—A case is described in which jacksonian seizures could be induced on the right side by various stimuli and movements on the same side. A study has been made of the characteristics of the effective stimuli and movements. Application of cocaine to the conjunctival sac of the right eye diminished the number and intensity of the reflex convulsions. The effect was both immediate and permanent. The spontaneous seizures of the patient were also favourably influenced by this procedure. (R. M. S.)

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*Primary Cortical Centres for Movements of Upper and Lower Limbs in Man: Observations Based on Electrical Stimulation. J. E. Scarff. 243.
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Meningioma in a Child. J. J. Keegan. 439.

Primary Cortical Centres.—It has long been commonly accepted in the literature and in the standard textbooks of anatomy that the primary cortical centres for the lower extremity in man were situated on the lateral convexity of the cerebral hemisphere. A critical review of the literature, however, indicates that this concept became established on the basis of a wholly inadequate number of observations made on the human brain—in fact, largely on observations made on the brains of experimental animals. Observations made by the author as a result of electrical stimulation along the superior mesial border of the human cerebrum in 14 consecutive cases indicate that the primary motor area for the upper extremity commonly extends upward on the lateral surface of the cerebral hemisphere as far as its superior mesial border, while the leg, as a rule, is represented only on the mesial surface of the cerebrum. An upward " migration " of the primary motor strip, unique in man, is implied by the observations reported here. It seems probable that this has been influenced by two factors: (1) " liberation " of the upper extremity from the routine burden of locomotion, with its consequent elaboration of new and highly complex functions; and (2) acquisition of speech and other forms of symbolic expression. These new functional acquisitions have been accompanied by corresponding expansion of the cortical areas representing the tongue, mouth, lips, and upper extremity, with the result that the cortical representation for the leg has been crowded farther and farther upward on the lateral surface of the hemisphere until it was finally pushed " over the top " onto the mesial surface of the hemisphere. Focal contractions of the rectal sphincter, produced by stimulation of the mesial surface of the cerebral hemisphere, are here reported for the first time. (R. M. S.)

Intracranial Tumours and Epilepsy.—The slowly growing neoplasms have a higher incidence of secondary epilepsy than the rapidly growing tumours, probably because death terminates the history sooner in cases of the latter type. Seizures form a first symptom also more frequently in cases of the slowly growing tumours. Infiltrating and encapsulated tumours, if they are equally slow growing, have an approximately equal incidence of seizures. Operative removal gives complete relief from seizures twice as often in cases of encapsulated tumours as it does in cases of infiltrating tumours. In the Montreal neurological clinic the percentage of " cure " of seizures by operative removal of encapsulated tumours is about the same as that from excision of focal cerebral scars for the relief of epilepsy. Abscesses of the brain are apt to produce seizures at an early stage and again after the formation of a healed scar. Subdural hæmatomas have a relatively low incidence of seizures, and the attacks even then seem to be due to cerebral injury that may have resulted from trauma rather than to the hæmatoma itself. (R. M. S.)

Experimental Headache and Migraine.—Apparently the threshold for histamine headache is lower in persons subject to chronic recurrent headache than in those not so afflicted and in patients subject to migraine attacks the type of headache produced by histamine is frequently similar to migraine headache. No evidence was discovered that the cranial vascular tree in patients subject to hemicranial migraine headache is unilaterally hypersensitive to histamine. (R. M. S.)

Corpus Striatum.—Stimulation of the caudate nucleus in cats inhibits movements of the skeletal muscles, probably induced by the corticospinal system. The effect is best noted on the ipsilateral side. Stimulation of the caudate nucleus inhibits bladder tone and tends to depress respiration and reduce activity of the sweat glands. Little evidence for somatic localization of these effects within the corpus striatum has been found. (R. M. S.)

E.E.G. Studies of Head Injury.—In addition to emphasizing the need of applying the electroencephalographic method to all varieties of cerebral trauma the authors' studies indicate that the encephalogram provides a sensitive measure of recovery. (R. M. S.)

Dislocations in Metrazol Convulsions.—For the avoidance of fractures and dislocations in the convulsions caused metrazol shock therapy the author advo-

cates a method of manual restraint. At least four assistants are required. (R. M. S.)

Human Behaviour after Removal from Frontal Lobes.—Before operation an injury in the frontal region and the formation of scar tissue had resulted in serious behavioral abnormalities. Further destruction, surgically, instead of aggravating the symptoms, made them disappear. The case appears to establish that bilateral removal in man of the anterior third of the frontal lobes may have no obvious effect on human intelligence or personality. The absence of gross deterioration does not rule out, however, the possibility that in such features as learning in social situations or in initiative and the ability to plan and organize one's affairs impairment may be found. (R. M. S.)

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*Vascularization and Vulnerability of the Cornu Ammonis in the Opossum. E. Scharrer. 483.
Constitutional Differences between Deteriorated and Non-deteriorated Patients with Epilepsy: iv. The Handwriting. H. A. Paskind and M. Brown. 507.
*Action Potentials of Muscles in Athetosis and Sydenham's Chorea. P. F. A. Hoefer and T. J. Putnam. 517.
*Spontaneous Cerebral Ventriculostium. W. H. Sweet. 532.
One Hundred Cases of a Condition Diagnosed as Acute Encephalitis: A Clinicopathologic Study. A. Adler. 541.
*Comparative Study of Metrazol Treatment and Control Observations of Schizophrenia. J. Notkin, F. J. DeNatale, C. E. Niles, and G. Wittman. 568.
*Spastic Pseudosclerosis (Disseminated Encephalomyelopathy: Corticopallidospinal Degeneration): Familial and Non-familial Incidence (a Clinicopathologic Study). C. Davison and A. M. Rabiner. 578.
Myeloradiculoneuritis with Cell-Protein Dissociation. D. Shaskan, H. A. Teiteibaum, and L. D. Stevenson. 599.
Vestibular Reactivity in Schizophrenia. A. Angyal and N. Blackman. 611.

Special Articles:
Physiologic Aspects of Schizophrenic Withdrawal. A. Angyal, H. Freeman, and R. G. Hoskins. 621.

Case Reports:
*Subarachnoid and Intracranial Hemorrhages due to Metrazol. H. N. Roback and C. W. Miller. 627.
Defective Closure of the Neural Tube: A Case of Involvement of the Central Olfactory, Trigeminal Mesencephalic, Visual Reflex, Auditory and Cerebellar Systems. H. S. Rubinstein and W. Freeman. 636.

Vascularization of Cornu Ammonis in Opossum.—Carbon monoxide poisoning in the opossum affects primarily the cornu ammonis and its vulnerability is explained by a simple hydrodynamic effect of the drop in blood pressure and the dilatation of the blood vessels on the velocity of blood flow under the influence of carbon monoxide. Whereas in blood vessels branching dichotomically the fall in the blood pressure is distributed equally, in the rakelike pattern of the vascular system of the cornu ammonis the blood pressure can drop locally below a critical level before this condition occurs in the rest of the brain. On account of the sluggish flow of blood, the nerve cells in these areas are exposed to lack of oxygen and to the poisonous effect of carbon monoxide longer and more severely than are those in areas in which the circulation has not yet reached so low a point. The suggestion is made that the results obtained in the opossum may lend themselves to a satisfactory explanation of the selective vulnerability of Sommer's sector of the cornu ammonis in man, which has a rakelike vascular pattern of the type seen in the opossum. (R. M. S.)

Action Potentials of Muscles in Athetosis.—Action potentials of muscles in patients with athetosis and Sydenham's chorea have been studied. Motor unit discharges are asynchronous and polyrhythmic in simultaneous leads during both involuntary and voluntary movements. In this respect they resemble normal voluntary innervation. Antagonists are in almost constant, simultaneous innervation, which may be steady or irregular in either muscle, during both involuntary and voluntary movements. During periods of rest no indication of basic or " tonic " innervation is noticed in the muscle. During occasional periods of innervation of the protagonist alone no activity in the antagonist is seen. This seems to indicate that in cases of uncomplicated type the " stretch " reflex mechanism is not active, as in spasticity. In cases in which spastic paraplegia is a complication a tendency to synchronous motor unit discharge is seen, but the simultaneous innervation of antagonists is the same in these cases as in those of pure athetosis. Alternating tremor may be found as a complication of both diseases. This is considered to be caused by involvement of a different pathological mechanism. (R. M. S.)

Spontaneous Cerebral Ventriculostium.—Two cases are reported in which there was a spontaneous rupture connecting a ventricle with the surface of the brain. In the first case the rupture through the lamina terminalis permitted a remission in the patient's symptoms for 9 years, and the abnormal ostium was still patent 11 years after the presumed time of its development. This case constitutes the longest clinical demonstration on record of the efficacy of ventriculostomy of the third ventricle for the relief of obstructive hydrocephalus arising from occlusion of the aqueduct of Sylvius or the fourth ventricle. In the second case a rupture through the medial wall of one lateral ventricle did not relieve the patient's symptoms, since no communication was established with the subarachnoid space. (R. M. S.)

Metrazol Treatment and Schizophrenia.—Various degrees of improvement took place in 18 per cent. of a group of 100 schizophrenic patients. This is a much lower percentage than that generally reported,

but in 78 per cent. the psychosis had lasted for more than 18 months. None of the treated or the control patients recovered. (R. M. S.)

Spastic Pseudosclerosis.—Four cases of spastic pseudosclerosis are reported, in three of which the disease occurred in members of the same family. Clinically, disease of the pyramidal and extrapyramidal systems and the anterior horn cells and mental symptoms were present in all. In one instance there were also sensory disturbances. The mental symptoms in all of these cases appeared last. Hispathologically, changes were observed in the frontal, premotor, motor, and parietal convolutions, in the pyramidal and extrapyramidal systems and in the lower motor neurons. (R. M. S.)

Subarachnoid Hæmorrhage Due to Metrazol.—A case is described of death due to subarachnoid and intracerebral hæmorrhages following the ninth injection of metrazol (5 c.c.). It is believed that the hæmorrhages were due to increased permeability of the vessel walls caused by the toxic effects of metrazol and degeneration of the liver. The opinion is expressed that, since therapy with metrazol appears to be less dangerous than was originally believed, its contraindications are few, and psychotic patients with some physical complications should be given the benefit of metrazol shock therapy. (R. M. S.)

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*Experimental Studies on Headache: Further Analysis of Histamine Headache and its Pain Pathways. G. A. Schumacher, B. S. Ray, and H. G. Wolff. 701.
*The Human Pyramidal Tract: ii. A Numerical Investigation of the Betz Cells of the Motor Area. A. M. Lassek. 718.
*Changes in the Nervous System Following Carbon Disulfide Poisoning in Animals and in Man. B. J. Alpers and F. H. Lewy. 725.
Surgical Division of Commissural Pathways in the Corpus Callosum: Relation to Spread of an Epileptic Attack. W. P. Van Wagenen and R. Y. Herren. 740.
*Faradic Shock in Treatment of Functional Mental Disorders: Treatment by Excitation followed by Intravenous Use of Barbiturates. N. J. Berkwitz. 760.
*Connections of the Red Nucleus. J. W. Papez and W. A. Stotler. 776.
*"Spinal Dysaphism": Spina Bifida and Myelodysplasia. B. W. Lichtenstein. 792.
*Advantages and Danger of Combined Anoxic and Insulin Shock: Report of Animal Experiments with a Possible Method of Treatment for Schizophrenia. J. Tannenberg. 811.
Case Reports:
Behaviour of Electrolytes in Familial Periodic Paralysis. J. W. Ferebee, M. K. Gerity, D. W. Atchley, and R. F. Loeb. 830.
*Familial Paroxysmal Choreoathetosis: Preliminary Report on a hitherto Undescribed Clinical Syndrome. L. A. Mount and S. Reback. 841.
Chronic Encephalitis: Pathologic Report of a Case with Protracted Somnolence. R. B. Richter and E. F. Traut. 848.
Diabetes Insipidus. T. H. McGavack, J. W. Benjamin, and S. Liebowitz. 867.
Resorption of Intracranial Gumma Under Electroencephalographic Control. M. Rheinberger and J. Siris. 879.

Experimental Studies on Headache.—Of 15 subjects in whom afferent impulses from the superficial tissues of the scalp on one side were blocked by procaine, histamine headache in four and headache due to pneumœncephalographic examination in 11 were the same on the two sides of the head. In 12 subjects obliteration of the circulation of the scalp by a blood pressure cuff modified the intensity of the histamine headache. That the reduction in pain was due to raising the pain threshold by introducing a second pain (the tight cuff) is offered as a likely hypothesis. Of five subjects, obliteration of the temporal artery by manual compression reduced the intensity of the histamine headache on that side in two but had no effect in three. Complete subcutaneous infiltration with procaine hydrochloride of half the anterior part of the scalp (frontal, parietal, and temporal areas on one side), including presumably all the vessels of the scalp in that area, did not prevent severe histamine headache in the frontotemporal region, bilaterally, which was of equal intensity on the two sides. Injection of histamine directly into the temporal artery resulted in homolateral temporoparietal headache in two subjects. Ligation of the temporal artery on one side in four subjects and of the middle meningeal artery on one side in seven subjects did not influence the intensity of the headache experienced on the two sides after injection of histamine. In seven subjects who had partial section of the sensory root of the fifth cranial nerve on one side (resulting in unilateral analgesia of the lower part of the face in six) histamine headache occurred bilaterally. In seven of eight patients who had complete section of the sensory root of the fifth cranial nerve (resulting in unilateral hemianalgesia of the face and anterior half of the scalp), histamine headache was not induced on the denervated area, but did occur elsewhere in the head. In a subject with complete hemianalgesia of the face and head (resulting from a head injury), strictly unilateral hemicrania on the normal side of the head was induced by histamine. Histamine headache was absent in the back of the head on one side, but was present elsewhere in the head in two subjects with lesions of the cervical portion of the cord, causing unilateral occipital analgesia. Section of the seventh and the ninth cranial nerve, respectively, in two subjects did not affect the bilateral equality of the headache induced by histamine. Section of both sympathetic trunks in two subjects (cervical portion in one and thoracic portion in the other) had no effect on subsequently induced histamine headache. (R. M. S.)

Human Pyramidal Tract.—The Betz cells

can contribute but 2 or 3 per cent. of the fibres found within the pyramidal tract. The size rather than the number of the Betz cells suggests that they may be of importance in pyramidal conduction. (R. M. S.)

Carbon Disulphide Poisoning.—This study includes a survey of the changes in the nervous system in man and in experimental animals following carbon disulphide poisoning. A comparison of the two discloses the fact that in the human nervous system one finds scattered changes in the ganglion cells of the cerebral cortex of varying degree, depending on the severity of the intoxication, disease of the basal ganglia and peripheral nerves and evidence of vascular involvement; in the experimental animal there are more extensive damage to the cerebral cortex and basal ganglia injury of the Purkinje cells, vascular changes, minor damage to the spinal cord and involvement of the peripheral nerves. The changes in the ganglion cells are nonspecific and are merely a manifestation of injury by a noxious agent. The difference in the changes in man and in the experimental animal may be explained, in part at any rate, by the difference in length and degree of exposure to the chemical. (R. M. S.)

Commissural Pathways in Corpus Callosum.—Section of the commissural pathways contained in the corpus callosum may be carried out without any untoward effect on the patient. Such a section may serve to limit the spread of an epileptic wave to the opposite hemisphere. When such limitation occurs, the patients do not seem to lose consciousness or have generalized convulsions. When there are multiple areas from which an epileptic seizure may originate, possibly simultaneously, section of commissural pathways between hemispheres may not have any influence on the seizures. (R. M. S.)

Faradic Shock and Functional Mental Disorders.—The author claims to have secured good results in various types of mental disorder by the employment of a faradic current as a form of shock therapy. (R. M. S.)

Connections of Red Nucleus.—The authors' studies deal largely with the question of pallidorubral connections through the medium of the prerubral field H or nucleus campi Foreli, with the origin and ending of the fasciculus thalamicus, with the segments of the red nucleus and with the origin and destination of descending rubral tracts. Taken together, these stations and pathways appear to form a descending pallidal system, which is part of the extra pyramidal equipment of the brain stem with cortical, pallidal, and cerebellar interconnections. (R. M. S.)

"Spinal Dysraphism."—The author describes three cases illustrating many of the characteristic anomalies of the spinal cord belonging to the spinal bifida, or dysraphic group. (R. M. S.)

Combined Anoxic and Insulin Shock.—The common therapeutic factors of the various modern shock and drug therapies for schizophrenia is held to be the general functional readjustment of the central nervous system after the multiple microdestruction of brain tissue that is unintentionally accomplished by all these methods. (R. M. S.)

Familial Paroxysmal Choreoathetosis.—The authors describe what they believe to be a hitherto undescribed clinical syndrome, the essential features of which are the paroxysmal occurrence of attacks of choreoathetosis and the marked familial background. (R. M. S.)

BRAIN

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Sir Henry Head, M.D., F.R.C.P., F.R.S. 1891–1940. Editor of "Brain," 1910–1925. 205.
*An Analysis of 1,433 Cases of Paroxysmal Trigeminal Neuralgia (Trigeminal-Tic) and the End-Results of Gasserian Alcohol Injection. W. Harris. 209.
*Optic Atrophy Associated with Pernicious Anæmia. J. W. Aldren Turner. 225.
*A Form of Familial Presenile Dementia with Spastic Paraplegia. C. Worster-Drought, J. G. Greenfield, and W. H. McMenemey. 237.
*The Relation of Atrophy to Fibrillation in Denervated Muscle. D. Y. Solandt and J. W. Magladery. 255.
*Experimental Lesions in the Basal Ganglia of the Cat. E. G. T. Liddell and C. G. Phillips. 264.
*Familial Pes Cavus and Absent Tendon-Jerks: Its Relationship with Friedreich's Disease and Peroneal Muscular Atrophy. J. D. Spillane. 275.

Trigeminal Tic and Gasserian Ganglion Injection.—Thirty years' experience of alcohol injection in trigeminal neuralgia is reviewed. 1,433 cases were treated, of which 457 were followed up. 316 of the 457 had no recurrence of pain for 3 years or more, and 12 for over 20 years. Local infection is thought to be the usual cause of tic doloreux, and other factors, such as heredity and preceding disease are analysed. Some of the complications of injection are discussed. (D. J. W.)

Optic Atrophy and Pernicious Anæmia.—Visual failure was recognized in three early cases of pernicious anæmia. It was associated with primary optic atrophy and small oblong central scotomata spreading to the blind spot. Useful vision slowly returns if the anæmia is adequately treated. (D. J. W.)

Familial Presenile Dementia with Spastic Paralysis.—An unusual case of presenile dementia is described. There was widespread demyelinization with peculiar degenerative changes around small blood vessels. The parenchymatous changes were thought to be secondary to the vascular damage, for which no cause could be found. Eleven cases were found in five generations followed in one family. The course of the disease was similar in each and one autopsy is reported. The syndrome has features similar to other recognized forms of presenile dementia but seems to be a separate entity. (D. J. W.)

Relation of Atrophy to Fibrillation in Muscle.—Atrophy following motor denervation of skeletal muscle occurs in the absence of fibrillation. It is therefore not due to the fibrillary activity. (D. J. W.)

Experimental Lesions in Basal Ganglia.—Lesions in the basal ganglia of 26 cats caused slight hypertonia of the extensor muscles of the contra-lateral limbs. This was associated with a delayed flexor reflex, defective placing reactions, ipsilateral flexor hypertension, and defective closure of the opposite eyelid. The extensor hypertonia was temporarily reduced by deafferentiation. (D. J. W.)

Familial Pes Cavus and Absent Tendon Jerks.—Roussy and Lévy's syndrome is an intermediate subgroup of the heredofamilial degenerations of the cord and cerebellum, of which Friedreich's disease and the muscularatrophy of Charcot-Marie-Tooth are examples. (D. J. W.)

CLINICAL SCIENCE

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The Excretion of Pregnandiol and the Corpus Luteum. C. L. Cope. 217.
Venous Pulsation in the Orbit. T. Lewis. 243.
Observations on Periarteritis Nodosa. R. T. Grant. 245.
The Adjustment of Bloodflow to the Affected Limb in Arteriovenous Fistula. T. Lewis. 277.
Pituitary-Like Factors in the Blood and Urine of Diabetic Patients and of Animals Treated with Pituitary Extracts. H. P. Himsworth and R. B. Kerr. 287.
*Somatic Simulating Visceral Pain. J. H. Kellgren. 303.
A Simplification of the Evans Blue Method of Blood Volume Determination. C. R. Harington, E. E. Pochin, and J. R. Squire. 311.
Thyrotropic Hormone in the Blood. H. B. Collard, F. H. Mills, F. F. Rundle, and E. P. Sharpey-Schafer. 323.
*An Instrument for Measuring the Quantity of Blood and Its Degree of Oxygenation in the Web of the Hand. J. R. Squire. 331.

Somatic Simulating Visceral Pain.—A series of cases illustrates the similarity of pain arising from somatic and visceral disease. Thus somatic disease such as senile kyphotic deformities may give pain simulating angina pectoris, peptic ulcer, renal, or biliary disease. The test of local anæsthesia may clinch the diagnosis of somatic disease. (W. M. H.)

Instrument for Measuring Blood.—The quantity of blood and its degree of oxygenation may be calculated from the amounts of red and infra-red light transmitted, readily measured in the apparatus described. (W. M. H.)

JOURNAL OF ANATOMY

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The Nature of the Soft Palate. F. W. Jones. 147.
An Experimental Study of the Morphogenesis of Intersexuality. S. Zuckerman and J. R. Groome. 171.
*The Projection of the Cerebral Cortex on the Pons and Cerebellum in the Macaque Monkey. S. Sunderland. 201.
*On the Relative Positions of the Hippocampus and the Corpus Callosum in Placental Mammals. F. Goldby. 227.
*Corticofugal Degeneration Following Thermocoagulation of Areas 4, 6, and 4-s in Macaca Mulatta. W. J. C. Verhaart and M. Kennard. 239.
*The Innervation of the Musculature of the Tongue. G. Weddell, J. A. Harpman, Lambley, and L. Young. 255.
*The Development of Nerve-Endings in the Respiratory Muscles of the Sheep. L. M. Dickson. 268.
The Development of Synovial Joints. J. Whillis. 277.
The Evolution of the Haversian Pattern in Bone. G. N. C. Crawford. 284.

Projection of Cerebral Cortex on Pons and Cerebellum.—(1) The topography of the pontine nucleus is described. (2) The experimental investigations show that (*a*) cortico-pontine fibres take origin in the frontal, parietal, occipital, and temporal lobes of the brain and terminate in the rostral three-quarters of the ipsilateral pontine nucleus. (*b*) The fronto-pontine tract receives fibres from area 6, but probably none from areas 8 and 9. These were the only fields of the frontal lobe investigated. The tract occupies the medial segment of the cerebral peduncle and terminates chiefly about the dorsal and medial portion of the nucleus in the rostral half of the pons. (*c*) The parietal, occipital, and temporal fibres are associated in a common pathway which occupies the lateral segment of the cerebral peduncle and terminates chiefly about the ventral and lateral aspects of the rostral three-quarters of the pontine

nucleus, the parietal fibres terminating more distally than the remainder. The cortical fields giving origin to these fibres and the relative contributions from those fields are discussed. (*d*) The rostral half of the pontine nucleus projects chiefly on to the contralateral lobus medius of the cerebellum. There is no strict projectional localization in the sense that a particular part of the nucleus projects exclusively to any specific cerebellar area. All aspects of the nucleus appear to project diffusely over the surface of the lobus medius. In correlating these findings the author says that it may be assumed that the cerebral cortex projects to the contralateral lobus medius of the cerebellum, which represents the neo-cerebellum, in such a way that the various parts of the lobe have equivalent values anatomically and physiologically, and that any differentiation in the nucleus is more dependent on its cortical relationships than on its cerebellar connections. (G. W.)

Relative Positions of Hippocampus and Corpus Callosum in Placental Mammals.—The relationship between the hippocampal formation or its vestiges and the corpus callosum and psalterium is from transverse serial sections stained by toluidin blue, in a bat and the cat. Similar observations were made in the rat and mouse, using, in addition, sagittal and horizontal sections and a silver impregnation method as a fibre stain. The investigations lead to the conclusion that the corpus callosum and psalterium of placental mammals lie morphologically ventral to the hippocampus and its vestiges. The relationship is most clearly seen in the bat. In mammals with a larger corpus callosum (e.g. cat) a hippocampal flexure is formed beneath the hinder part of the corpus callosum, as Elliott Smith originally described. In the rat and mouse this flexure is less clearly seen. In general the findings support the theory of Elliott Smith regarding the origin of the corpus callosum and the homologies between the placental and marsupial commissures which he established. No evidence has been found for Abbie's (1939) view that the corpus callosum has grown through subicular cortex above the hippocampal formation. (G. W.)

Corticofugal Degeneration following Thermocoagulation.—Following identification of areas A6, A4s, and A4 (A=arm region) laminar thermocoagulation within each region will produce Marchi degeneration localized to fibre tracts from each region; these have been traced to their subcortical destinations. All tracts previously well established by other authors for the precentral gyrus as a whole were found in the present investigation for the individual areas and no new connections were established. Fibres from areas A6, A4s, and A4 were found ending chiefly in nasal pontine nuclei, substantia nigra, and thalamus; no fibres could be traced to the red nucleus. The existence of cortico-caudate fibres was not definitely established. With the exception of the cortico-spinal tract from A4 no tract was found in any one cortical area which did not appear in the other two (6 and 4s) as well. The fibres from each area are arranged in a definite pattern throughout their course in the internal capsule; and they have a similar organization in the pes pedunculi, and as they project upon the various subcortical nuclei. (G. W.)

Nerve-Endings in Respiratory Muscle.—The muscle fibres and nerve-endings in the intercostal muscles and diaphragm of 12 sheep fœtuses are described. The formation of the muscle spindle is found to begin about the 45th day of gestation and to be well advanced by mid-term (80 days). Motor end-plates are not found at 111 days and are present in simple form at 137 days. The findings are correlated with the observations of other workers that sustained movement and inhibition of respiratory muscle are present long before the earliest development of motor end-plates. (G. W.)

Innervation of Tongue Musculature.—The innervation of the intrinsic and extrinsic musculature of the tongue was studied histologically by a modified methylene blue technique in a series of 37 normal and 11 operated rats and 1 rabbit in which the hypoglossal and lingual nerves and the cervical sympathetic chain had been resected alone or in various combinations. The staining technique is based upon the injection of measured quantities of dye into tissues of which the circulation is maintained. The method described is applicable to the musculature of the tongue in rats and rabbits and the skin of the ear in the rabbit. No sensory endings were found in the intrinsic muscles of the tongue. No muscle spindles were found in the hypoglossus or genioglossus muscle. Sensory endings of a tension-recording type were found at the origin of the genioglossus muscle. No nerve cells were found along the course of the hypoglossal nerve in the tongue. Sympathetic fibres run in the hypoglossal nerve to reach the blood vessels in the tongue. No accessory nerve endings to muscle fibres or motor end-plates were found. The sympathetic ground plexus, periterminal network and terminal reticulum are considered to be reticular connective tissue. No nerve nets were observed. Dilatation of the pupil on stimulation of the hyperglossal nerve in rats under light ether anæsthesia was found to be due to stimulation of the sympathetic fibres of the hyperglossal nerve. Proprioception, taste, pain, and touch were tested on the tongue, lower gum, and lip in 19 human subjects in which the lingual and inferior alveolar nerves had been unilaterally and

bilaterally infiltrated with novocaine, or in which the mucosa of the tongue, oral pharynx, and palate had been painted with " decicain " or cocaine. In cases in which the lingual nerve was anæsthetized by infiltration the area of ageusia was limited to the anterior two-thirds of the tongue and there was no overlap in the midline. Pain and touch were found to overlap in the midline in the region of the lower gum. This was confirmed in a case of central root division of the trigeminal nerve. All forms of sensation tested in the anterior two-thirds of the tongue were found to be abolished on complete anæsthetization. There was no ataxia or tendency to bite the tongue after complete anæsthetization, although articulation was difficult. The mechanism of proprioception is discussed in the light of the anatomical and clinical findings and recent physiological work. (G. W.)

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An Experimental Study of the Development of the Amphibian Cloaca. R. J. O'Connor. 301.
Studies of the Regeneration of Lymphatic Vessels. J. H. Gray. 309.
*The Spinal Accessory Nerve in the Sheep. G. J. Romanes. 336.
*The Intramural Nervous System of the Small Intestine with Special Reference to the Innervation of the Inner Subdivision of its Circular Muscle. Pei-Lin Li. 348.
The Development of the Patella. R. Walmsley. 360.
Transmutation of Vertebræ in the Lumbosacral Region of the Human Spine. M. Young and J. G. H. Ince. 369.
A Radiographic Comparison of the Male and Female Pelvis. M. Young and J. G. H. Ince. 374.
*The Fibre Components of the Laryngeal Nerves of Macaca Mulatta. R. J. Brocklehurst and F. H. Edgeworth. 386.
The Comparative Morphology of the Platysma. A Comparative Study of the Sphincter Colli Profundus and the Trachelo-Platysma. G. S. Lightoller. 390.
The Comparative Morphology of the M. Caninus. G. S. Lightoller. 397.
Cephalomelus: A Rare Tumour in a Lamb. D. V. Davies. 403.

Spinal Accessory Nerve in Sheep.—Descriptions of the macroscopic arrangement of the spinal accessory nerve in the sheep are given, with special reference to its relationship to the cervical spinal nerve roots. Two distinct stages of medullation exist in the spinal accessory nerve—(*a*) fibres from the motor nucleus of this nerve are already well medullated in the 78-day-old sheep fœtus ; (*b*) a second set of fibres connecting the spinal accessory nerve with a longitudinal tract visible as a caudal continuation of the solitary tract in pre-myelin stages, begins to medullate in an 84-day-old sheep fœtus, and reaches adult medullation by the 124th day of fœtal life, by which time it shows a medullated continuity with the solitary tract not previously visible. Ganglionic cells of a sensory type have been demonstrated on the intra-dural part of the spinal accessory nerve and on one or two of its more cephalic rootlets. It is suggested that the spinal accessory nerve of the sheep is a mixed nerve whose medullation is precocious. It appears to be related to the visceral rather than to the somatic cell column, as suggested by its connections with the solitary tract and the close relation between its motor nucleus and the nucleus ambiguous. (G. W.)

Intramural Nervous System of Small Intestine.—The circular muscle of the small intestine of many vertebrates consists of a thick external and a thin internal inner layer. The external layer is supplied by the tertiary branches of Auerbach's plexus and a cell net of well-developed interstitial cells of Cajal comprising the " plexus terminal or interstitial " of van Esveld. The inner layer is specially rich in nerve fibres which are mainly of local origin, being the protoplasmic processes of a rather primitive type of interstitial cell of Cajal. The interstitial cells of Cajal are well-developed in the space between the circular and longitudinal muscles and in the external layers of the circular muscle. Definite relationships between the interstitial cells of the nerve fibre strands and the ganglion cells of Auerbach's plexus, and the muscle cells are emphasized. The interstitial cells of Cajal are in all probability ganglion cells, as suggested by Cajal, Böcke, and Leenwe. Since the inner layer of the circular muscle is rich in primitive nervous elements, it may be considered as neuro-muscular in nature and may have definite relations to irritability, conduction, and rhythmic contractions. Catel's hypothesis of interstitial innervation receives support from these observations. (G. W.)

Fibre Components of Laryngeal Nerves.—Investigations were carried out on intact animals and in one in which the roots of the left vagus nerve and its radix accessoria s. bulbar accessorius had been divided proximally to the jugular and rodose ganglion 33 days previously. The fibre components of the nerves are recorded and discussed. (G. W.)

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*Observations on the Neurohistological Basis of Cutaneous Pain. The late H. H. Woollard, G. Weddell, and J. A. Harpman. 413.
*The Connexions of the Inferior Collicus and of the Dorsal Nucleus of the Lateral Lemniscus. The late H. H. Woollard and J. A. Harpman. 441.
Differentiation of Pituicytes in the Human Fœtus. W. M. Shanklin. 459.
Mounting Media and the Fading of Histological Preparations. F. Davies. 464.
*The Nervous and Vascular Relations of the Pineal Gland. W. E. Le Gros Clark. 471.
The Paranasal Sinuses of the Anthropoid Apes. A. J. E. Cave and R. W. Haines. 493.
A Note on the Length of the Basilar Membrane in Man and in Various Mammals. J. A. Keen. 524.

*Thalamic Degeneration Induced by Temporal Lesions in the Cat. W. H. Waller. 528.

Neurohistological Basis of Cutaneous Pain.—Pressure, warmth, touch, cold, and pain are represented in the skin in punctate form. The theory of punctate sensibility must be interpreted from a three-dimensional point of view. Multiple spots from which one of the primary modalities of sensation can be aroused occur within the area of skin supplied by a single specific sensory neurone. Cutaneous pain is subserved only by the finer medullated and non-medullated nerve fibres bearing free nerve endings. These fibres are specific and arranged in a plexiform interlocking manner. Non-medullated nerve fibres derived from different neurones often lie within the same neurilemma sheath. There are regional differences in the disposition of, and in the area supplied by, the terminal nerve plexus and endings derived from a single dorsal root ganglion cell subserving pain. Pain can be aroused from the deeper layers of the epidermis and the superficial layers of the dermis. Several varieties of cutaneous pain can be aroused by a single stimulus depending upon the nature of the stimulus and the region of the body stimulated. All varieties of cutaneous pain are subserved by the same nerve apparatus. The "accessory" innervation to encapsulated touch receptors and to nerve endings subserving pressure, cold and proprioception from tendon is morphologically similar to nerve fibres and endings subserving pain. Fine somatic nerve fibres bearing free nerve endings similar to those subserving pain in the skin occur in the adventitia of blood vessels. No nerve apparatus other than that subserving pain is involved in the production of hyperalgesia. "Nocifensor" reactions are mediated by the nerve apparatus subserving pain. There is no anatomical foundation for the usual conception with regard to "axone reflexes." The facts presented establish that cutaneous pain behaves in accordance with the doctrine of specific nervous activity. (G. W.)

Connexions of Inferior Collicus.—The connections of the inferior colliculus and of the dorsal nucleus of the lateral lemniscus were studied in four guinea-pigs and four cats. The method used were those of Marchi and its modification by Swank and Davenport. The majority of lateral fillet fibres arising from the cochlear nuclei end in the contralateral nuclei of the lateral fillet and cerebral nucleus of the inferior colliculus. Some fibres from the cochlear nuclei end in the homolateral nuclei of the lateral fillet and inferior colliculus. A few lateral fillet fibres end in the medial geniculate body. The termination of the lateral fillet fibres in the superior colliculus is problematical. In the guinea-pig the inferior brachium contains fibres derived from the homolateral inferior colliculus and a few lateral fillet fibres. In the cat it also receives fibres from the contralateral inferior colliculus through the inferior intercollicular commissure. The ascending fibres in the inferior brachium end in the caudo-ventral nucleus of the medial geniculate body. In two cats the findings suggest a spatial arrangement of the fibres in the inferior brachium. Tecto-pontine fibres arise, in the guinea-pig, from either the cranial pole of the inferior colliculus, the caudal part of the superior colliculus, the nucleus parabigerminus, or several of these centres. They course among the fibres of the lateral fillet and end in the ipsilateral lateral pontine nucleus. Tecto-pontine fibres arise, in the cat, from the caudal region of the superior colliculus. They form a bundle external to the lateral fillet and terminate as in the guinea-pig. Fibres from the ventro-lateral region of the inferior colliculus course medialwards and end in the central grey matter and possibly in the homo-lateral mesencephalic nucleus. A few fibres probably run from the inferior to the superior colliculus. The commissure of Probst, or dorsal commissure of the lateral fillet, receives fibres from the dorsal nucleus of the lateral lemniscus and collaterals from lateral fillet fibres. The fibres of the commissure end in the contralateral dorsal nucleus of the lateral lemniscus, dorsal nucleus of the brachium conjunctivum, and central nucleus of the inferior colliculus. Other fibres stated in the literature to arise from the inferior colliculus and dorsal nucleus of the lateral fillet have not been found. It is concluded that the midbrain auditory nuclei subserve very few reflex activities, being almost wholly sensory centres. It is suggested that the fibres from the temporal region of the cortex to the medial geniculate body and inferior colliculus control the sensory impulses received by these centres. (G. W.)

Nervous and Vascular Relations of Pineal Gland.—The pineal gland of the rhesus macaque contains a central cone of neurophil in which are embedded numerous large ganglion cells with branching processes. Contributing to this network of nerve fibres are perivascular plexuses accompanying branches of the choroidal arteries which penetrate the pineal gland from its lateral aspect and also a conspicuous fasciculus which can be traced to the apex of the pineal gland where it emerges as the nervous conarii. Fibres from the habenular and posterior commissures enter the substances of the pineal gland through its peduncle, but on tracing these through serial sections many are found to be merely aberrent commissural fibres which enter the peduncle on one side and leave it on the other. It is considered not improbable that all the fibres from the commissures which have been followed into the parenchyma of the pineal gland

may be of a similar nature. Some of the fibres of the posterior commissure certainly terminate in relation to the ependymal epithelium lining the posterior wall of the pineal recess and have shown regular beading and minute end-bulbs. The central cone of neurophil in the macaque epiphysis is pervaded by a rich capillary plexus. Elsewhere the gland shows no great vascularity. No system of blood vessels is present which links the pineal gland with cell connections in the epithalamus comparable to that which has been described in relation to the hypophysis and the hypothalamus. In the monkey a choroidal vessel extends up into the wall of the straight sinus where it ramifies in a subendothelial position. From this vessel recurrent twigs descend to enter the pineal gland at its apex. The nervous conarii in the monkey has been traced from the central cone of neurophil in the pineal gland into the wall of the straight sinus. Here it ramifies in a plexiform manner in a subendothelial position, its fasciculi usually having a close topographical relation to branches of the choroidal artery which are also found here. Some sections show a globular skein of nerve fibres in the pial tissue, between the pineal gland and the straight sinus resembling a sensory nerve ending. In the human pineal gland the nervous conarii has been recognized. It emerges from the tip of the gland and runs an uninterrupted and apparently unbranched course to reach the dura mater of the tentorium cerebelli. Here it runs back in the floor of the straight sinus occupying a subendothelial position. The nerve has been followed in serial sections for a distance of 20 mm. Its destination (in a peripheral direction) has not been determined. A formation of the arachnoid has been described in relation to the floor of the straight sinus where the great vein of Galen opens into it. This structure somewhat resembles a large arachnoid granulation of the usual type, but its stroma consists of dense pial tissue containing a sinusoidal plexus of blood vessels and several large blood sinuses. It has been termed the suprapineal arachnoid body. From its structure and disposition it is suggested that the suprapineal body may provide a ball valve mechanism whereby the venous return from the great vein of Galen is regulated and controlled. On its way to the dural floor of the straight sinus the nervous conarii in the human brain was found in two specimens to pass through the suprapineal body and traverse one of the blood sinuses therein. No evidence was found either in macaque or human material for the existence of the " ganglion conarii " as described by Pastori. (G. W.)

Thalamic Degeneration Induced by Temporal Lesions.—The location of the auditory area in the cerebral cortex of the cat was determined by comparing the positions of eight surgical lesions of the temporal cortex with the distribution of the resulting cellular degeneration in the medial geniculate bodies. Six cats were used, two having lesions on both sides. The auditory radiation from the thalamus ends in a cortical area including the middle cetosylvian gyrus and the dorsal parts of the sylvian and anterior eclo sylvian gyri, extending ventrally to the upper tip of the sylvian sulcus. The rostral tip of the medial geniculate body is connected to the rostral part of the auditory area in the upper end of the anterior eclosylvian gyrus. The fibres from the central and ventromedial part of the geniculate body including the large cell portion of the nucleus end in the lower part of the acoustic area in the sylvian gyri. (G. W.)

JOURNAL OF CLINICAL INVESTIGATION

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The Mechanism of the Excretion of Vitamin C by the Human Kidney at Low and Normal Plasma Levels of Ascorbic Acid. G. J. Friedman, S. Sherry, and E. P. Ralli. 685.
A Photoelectric Method for the Quantitative Determination of Erythrocyte Fragility. F. T. Hunter. 691.
On the Inactivation of Thrombin by Plasma Protein. J. D. Stewart and G. M. Rourke. 695.
Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome: A Metabolic Study. D. M. Wilson, M. H. Power, and F. J. Kepler. 701.
Effectiveness of Per-Oral Insulin in Human Diabetes. J. R. Murlin, C. N. F. Gibbs, M. J. Romansky, T. B. Steinhausen, and F. L. Truax. 709.
Bronchial Calibre Changes in Bronchiectasis. J. Greenfield. 723.
Studies in Rheumatic Disease. v. The Age of Onset of Primary Rheumatic Attack. R. L. Gauld and F. E. M. Read. 729.
Antibody Formation in Cases of Lobar Pneumonia with Sulfathiazole. Y. Kneeland and B. Mulliken. 735.
Relations of Effective Renal Blood Flow and Glomerular Filtration to Tubular Excretory Mass in Normal Man. W. Goldring, H. Chasis, H. A. Ranges, and H. W. Smith. 739.
Glomerular Dynamics in the Normal Human Kidney. H. W. Smith, H. Chasis, W. Goldring, and H. A. Ranges. 751.
*Proceedings of the Thirty-Second Annual Meeting of the American Society for Clinical Investigation Held in Atlantic City, N.J., May 6, 1940. 765.

Proceedings of Thirty-Second Annual Meeting.

Rôle of C.N.S. in Renal Hypertension.—No peripheral vasoconstrictor substance in the blood of rabbits with renal hypertension was found experimentally, and it is concluded that the normal vasomotor mechanism is used to maintain the high arterial pressure.

Neuromuscular Transmission in Humans.—The method, which is described, has been used in normal subjects and in patients with myasthenia gravis. The abnormal responses found in this disease are corrected after prostigmin administration.

Measurement of Intracranial Blood Flow.—The principle of the venous occlusion plethysmograph is utilized for the measurements, and results of hyperventilation and temporary increased intracranial pressure are similar to those previously recorded. Cerebral blood flow is diminished in paresis and cortical atrophy, while nicotinic acid causes an increase.

Intravenous Histamine and Ménière's Syndrome.—Intravenous histamine caused an improvement with no untoward effects. Various metabolic studies were also made.

Experimental Pernicious Anæmia.—Macrocytic anæmia with ataxia and degeneration of the sensory neurone occurred in a few animals deprived of yeast but which received a fixed diet of casein, sucrose, lard, cod-liver oil, salt, thiamin, riboflavine, and nicotinic acid.

Destruction of Thiamin by Unacidified Bile.—The patient with achlorhydria is shown to develop a thiamin deficiency unless more than the usual quantity is taken in. This deficiency is suggested as the explanation of cord changes in pernicious anæmia.

Migarine.—From experimental procedures it is inferred that migrainous headache does not arise primarily from the cerebral arteries, but chiefly from dilatation and stretch of external carotid artery branches. Further, that pre-headache phenomena result from cerebral vasoconstriction. (J. N. C.)

Vol. 19. No. 6. November 1940.

The Origin and Nature of Normal Human Synovial Fluid. M. W. Ropes, E. C. Rossmeisl, and W. Bauer. 795.
Excretion of Sodium Pregnanediol Glucuronidate in Urine of Normal Human Pregnancy. C. Bachman, D. Leekley, and H. Hirschmann. 801.
The Effect of Large Doses of Vitamin A, B, C and D on the Incidence of Upper Respiratory Infections in a Group of Rheumatic Children. A. G. Kuttner. 809.
Carbohydrate Metabolism in Addison's Disease. G. W. Thorn, G. F. Koepf, R. A. Lewis, and E. F. Olsen. 813.
Choline Esterase of Blood Cells and Plasma in Blood Dyscrasias, with Special Reference to Pernicious Anæmia. J. C. Sabine. 833.
Fat Metabolism in Diabetes Mellitus. W. C. Stadie. 843.
Basal Gastric Secretion as a Clinical Test of Gastric Function with Special Reference to Peptic Ulcer. A. L. Bloomfield, C. K. Chen, and L. R. French. 863.

JOURNAL OF NERVOUS AND MENTAL DISEASE

Vol. 92. No. 2. August 1940.

*Extrapyramidal Function. F. A. Mettler. 141.
Left-Sided Weakness, Blood Pressure Difference between the Two Arms and Left Optic Atrophy. A New Clinical Syndome? F. E. Weatherby and N. H. Wiley. 151.
Prolonged Coma after Insulin Hypoglycemia: Clinical Features and Treatment. D. Goldman. 157.
VII. Speech Studies in Cretins: Speech Sounds. S. L. Schreiber, I. P. Bronstein, and A. W. Brown. 169.
Insulin Therapy in Schizophrenia and the Reticulo-Endothelial System. G. M. Davidson. 193.
*Artificial Fever Therapy in Multiple Sclerosis. A. E. Bennett and M. D. Lewis. 202.

Extrapyramidal Function.—In cats hypertonicity is induced when the lower connections of the caudate nuclei are cut and it is increased by elimination of the red nuclei. Contralateral spasticity is further increased when the entire brain anterior to the red nucleus is removed. On the whole, the effect of the corpus striatum must then be inhibitory, for while the pallidum is shown on stimulation to produce plastic tonus it cannot produce spastic states, striatal disorders are accordingly interpreted. Thus in Wilson's disease with the gross changes in the striatum rhombencephalic rigidity is no longer inhibited and tremor is accentuated by volitional activity, while for paralysis agitans it disappears since the striatal link is not impassable. In Huntington's chorea the pallidal structures are released from the inhibitory mechanism of the striatum, but since they are relatively intact movements appear synergic. In animals athetoid movements are produced by stimulation in the region of the rubrospinal tract, ascending limb of brachium conjunctiva and the reticulospinal tract. The rubrospinal tract has nothing to do with athetosis. It may be modified by ablation of cortical area 6 or section of the reticulospinal tract. The authors consider athetosis may come from abnormal activity in tracts leading to the substantia nigra, inferior olive nucleus ansa peduncularis, and from area 6 to the globus pallidus. The tentative nature of explanations based on present experimental results is emphasized. (W. M. H.)

Sclerosis and Fever Therapy.—From a study of 51 cases followed for an average of 31 months it is concluded that fever therapy is of value only in early cases of short duration and slight severity. It is not recommended in intermediate or advanced cases. (W. M. H.)

Vol. 92. No. 3. September 1940.

Localized Non-suppurative Encephalitis Secondary to Infections of the Temporal Bone and Paranasal Sinuses. With a Report of Four Cases. J. C. Yaskin. 281.
Metrazol Remission in Severe Obsession-Compulsion Neurosis of Five Years' Duration. M. Zeifert. 290.
Two Cases Showing Tonic Neck Reflexes and Tonic Fits Following Vascular Lesions in the Brain Stem. A. B. King. 302.
*Observations and Results Obtained in the Hypoglycemic Treatment of Schizophrenia. A. R. Coyne. 309.
*The Threat of Mental Disease. I. S. Wile. 323.
Adipositas Cerebralis and Emaciatio Cerebralis. A. Gordon. 342.
Meningeal Permeability and Metrazol Therapy. B. Skorodin. 348.

Hypoglycemic Treatment of Schizophrenia.—An analysis of results of insulin therapy in 55 schizophrenic patients followed for periods of 6 to 12 months. In 75 per cent. of the cases the duration of the psychosis was less than 2 years and this group included all those who recovered (19 per cent.). 17 per cent. were improved, 63 per cent. unimproved. No patient ill more than 5 years showed improvement. Favourable response to treatment was generally evident in the 3rd–4th week, while no permanent improvement was seen in those who showed no response by the 6th week. (W. M. H.)

Threat of Mental Disease.—This review adduces interesting statistics on the incidence of mental disease, emphasizing the cues for prevention found in the high proportion among first admissions of psychoses accompanying cerebral arteriosclerosis, the rôle of psychoses in increasing mortality, the socio-economic factors in the genesis of mental disease. (W. M. H.)

Vol. 92. No. 4. October 1940.

Bilateral Cortical Thromboses. D. M. Palmer. 429.
Hypoglycemic Epilepsy. L. J. Robinson. 442.
*Degeneration of the Basal Ganglia Associated with Olivo-Ponto-Cerebellar Atrophy. C. D. Aring. 448.
Vigilance and the Vitalistic Hypothesis. S. E. Jeliffe. 471.
*Cerebellar Agenesis. H. S. Rubinstein and W. Freeman. 489.

Basal Ganglia Degeneration.—Degeneration of the basal ganglia proceeding to cyst formation was found in a subject who had shown for 22 years the symptoms of lenticular degeneration. The liver was not involved. Olivo-ponto-cerebellar atrophy, disclosed microscopically, had no clinical counterpart. A single disease process, involving basal ganglia, brain stem and spinal cord is suggested. Two siblings were similarly affected. (W. M. H.)

Cerebellar Agenesis.—Signs of cerebellar defect appeared only 2 years before death (æt. 71) in a case of marked cerebellar agenesis. The brain showed atheromatous infarcts over the cortex, a right-sided defect in the brain stem, and a cerebellum represented by a small flocculo-nodular lobe. The authors discuss compensation for cerebellar deficiencies and conclude that it was not needed in a subject of such constitutional inferiority as the one described. (W. M. H.)

JOURNAL OF NEUROPHYSIOLOGY

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J. G. Dusser de Barenne 1885–1940. 283.
*Hypothalamic Lesions and Pneumonia in Cats. E. W. Haertig and J. H. Masserman. 293.
*Progression Movements Elicited by Subthalamic Stimulation. W. H. Waller. 300.
Electrical Activity of the Lateral Geniculate of Cats following Optic Nerve Stimuli. G. H. Bishop and J. S. O'Leary. 308.
Integration of Locomotor Behaviour Patterns of the Hagfish. B. Campbell. 323.
*Effects of Heating Hypothalamus of Dogs by Diathermy. A. Hemingway, T. Rasmussen, H. Wikoff, and A. T. Rasmussen. 329.
*Rôle of Neocortex in Regulating Postural Reactions of the Opossum (*Didelphys virginiana*). R. B. Bromley and C. McC. Brooks. 339.
*Chemical Constitution and Anæsthetic Potency in Relation to Cortical Potentials. H. K. Beecher. 347.
Ocular Movements from the Occipital Lobe in the Monkey. A. E. Walker and T. A. Weaver. 353.
*Nature of the First Visible Contractions of the Forelimb Musculature in Rat Fetuses. W. L. Straus and G. Weddell. 358.

Hypothalamic Lesions and Pneumonia.—After lesions in the mid-hypothalamic area between the chiasm and mammillary bodies cats show unusual motor behaviour when held upright by the nape of the neck, attempting to leap high and clawing wildly until set upon all fours. A large proportion succumb to bronchopneumonia. They respond to infection with fever, but hyperthermia is not maintained in fluctuating environmental temperatures. (W. M. H.)

Progression Movements and Subthalamic Stimulation.—A C stimulation of the subthalamus in the region dorsal to the mammillary bodies causes in cats under nembutal walking and running movements. The locomotor point appears to be in Forel's field at the level of the subthalamic decussation. (W. M. H.)

Optic Nerve Stimuli and Electrical Activity.—The electrical activity in the region of the external geniculate the radiation and cortex following electrical excitation of the optic nerve was studied oscillographically in the cat. The geniculate and cortex are activated by the first group of the

fastest waves in the fibres of the optic nerve. Paired shocks show facilitation of the second responses at intervals of 2–15 m./sec. Facilitation is likewise found at the cortical level. Slow potentials suggesting after potentials are found in the cell layers of the geniculate. The cortical activity shows a depression followed by facilitation in phasic relationship to the alpha rhythm after a single volley. Further elucidation of the cortical response must therefore be in terms of the patterns of the fibre response and of the cortical receptivity. Fibres from the optic tract spread over much of the area bounded by the medial and lateral geniculate, the pretectal area and the superior colliculus. In general the larger fibres synapse in the anterior, the smaller in the posterior regions. (W. M. H.)

Hypothalamus and Diathermy.—Local hypothalamic heating was produced in normal dogs without anæsthesia by means of diathermy. Small gold electrodes had been placed on the anterior or posterior hypothalami with leads to the skin surface and at least a month allowed for recovery. Following local heating at the anterior area shivering was almost instantly suppressed and peripheral vasodilatation occurred; after like heating of the posterior hypothalamus there was only slight reduction of shivering and no peripheral vasodilatation. Panting was not induced by local hypothalamic heating. (W. M. H.)

Neocortex and Postural Reactions.—While the postural responses of hopping and placing are slower and less exact in the opossum than in the phylogenetically higher forms, they are shown by extirpation experiments to be dependent in part on electrically excitable areas of the neocortex. (W. M. H.)

Chemical Constitution and Anæsthetic Potency in Cortical Potentials.—The frequency of cortical waves in the anæsthetized cat's brain is related to the anæsthetic potency, diminishing with increase of the molecular weight of the alcohols and substitution of secondary and tertiary for the primary forms. (W. M. H.)

Forelimb Muscle Contractions in Rat Fœtuses.—Effective neuromuscular transmission (efferent) is shown in 16-day rat fœtuses although nerve endings are primitive in form. It is suggested that extra muscular factors, such as those due to the poor differentiation of the limb structures, may account for the high threshold, long time factor, and long duration of the earliest visible muscular contractions. The theory of a "myogenic" developmental phase is rejected. (W. M. H.)

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Activity in the Simplest Spinal Reflex Pathways. B. Renshaw. 373.
*Influence of Sensory Systems on Spontaneous Activity of Cerebral Cortex. F. H. Levy and G. D. Gammon. 388.
*Choline Esterase in Brain and Spinal Cord of Sheep Embryo. D. Nachmansohn. 396.
*Central Course of "Recurrent Sensory Discharges." D. H. Barron. 403.
*Intercortical Connections of Corpus Callosum as Indicated by Evoking Potentials. H. J. Curtis. 407.
*An Analysis of Cortical Potentials Mediated by the Corpus Callosum. H. J. Curtis. 414.
*Function of Mesencephalic Root of Fifth Cranial Nerve. B. Corbin and F. Harrison. 423.
Oculomotor Nerve and Reflex Dilatation of Pupil. W. D. Seybold and R. M. Moore. 436.
Movements Elicited from Precentral Gyrus of Adult Chimpanzees by Stimulation with Sine Wave Currents. M. Hines. 442.

Spinal Reflex Pathways.—In decerebrated cats the central reflex time for a homolateral ventral discharge following stimulation of a lumbar dorsal root varies between 0·65 and 1·0 m./sec. Ventral root discharges from direct stimulation of the central gray show that the synaptic delay at the motoneurones is similar. Large groups of motoneurones are typically discharged at particular central reflex times. (W. M. H.)

Sensory Systems and Cerebral Cortex.—Under nembutal anæsthesia the spontaneous activity of the cortex is dependent upon the integrity of the sensory pathways, disappearing when the brain stem is cut at the colliculi, the optic thalamus destroyed, or its cortical radiations severed. Discharges like the spontaneous bursts of activity appear throughout the cortex when sensory nerves, the thalamus or thalamo-cortical fibres are stimulated at rates 6–20 per min. Faster rates set up an after-discharge lasting several minutes. (W. M. H.)

Choline Esterase in Brain and Spinal Cord.—At an early stage in gestation (60–80th day) choline esterase is in high concentration in the spinal cord of sheep fœtuses while the amount in brain is low, rising rapidly during the final few weeks. This finding is correlated with the mainly local reflex character of the early movements in mammalian embryos. The enzyme is found concentrated at the nerve endings before end plates appear. (W. M. H.)

Recurrent Sensory Discharges.—Conduction of recurrent sensory discharges by collateral fibres of the type hitherto postulated would seem unlikely from experiments in rats. Rootlets carrying these discharges were identified and cut. The peripheral portions were found to show no evidence of degenerating fibres and action potentials could not be recorded from the central portion 3 days after section. (W. M. H.)

Intercortical Connections of Corpus Callosum.—In cats and monkeys single electrical shocks applied to one hemisphere give rise to potentials in the other hemi-

sphere generally most readily detected at the symmetrical point. In the monkey an exception is the operculum of the occipital lobe. Localized stimulation in certain areas may evoke potentials over a considerable portion of the corresponding contralateral area. These impulses are mediated by direct callosal fibres. (W. M. H.)

Cortical Potentials Mediated by Corpus Callosum.—The potential wave caused by stimulation of the contralateral hemisphere is diphasic, being surface positive for 15 m./sec. and negative for 75 m./sec. Nembutal obliterates the negative phase. Results from micro-electrodes inserted to various depths suggest that ascending fibres of the callosum ramify in the upper layers and end in the first layer where they synapse with descending interneurones which lead to deeper cortical layers. The ascending fibres contributed the surface positive component, the descending the negative. (W. M. H.)

Mesencephalic Root of Fifth Cranial Nerve.—Electrical potentials from the mesencephalic root of the Vth, localized with the Horsley-Clarke instrument, are elicited by pressure stimulation of the teeth and palate, and by stretching of the masticator muscles. Impulses in the alveolar and palatine nerves passing to the motor nucleus are probably inhibitory. No potentials from the IIIrd, IVth, or Vth nerves result from the stretch of the extrinsic ocular muscles. (W. M. H.)

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*The " Blue-Green " Region of the Spectrum. J. C. Hay and H. E. Roaf. 389.
The Weight of the Chromophore Carrier in the Visual Purple Molecule. E. E. Broda, C. F. Goodeve, and R. J. Lythgoe. 397.
*The Action of the Antidiuretic Principle of Posterior Pituitary Extracts on the Urine Excretion of Anæsthetized Animals. H. Heller. 405.
The Pituitary and the Insulin Content of Pancreas. R. E. Haist. 419.
*The Action of Some Amines Related to Adrenaline: Phenylallylamine, Phenylbutenylamine, Diphenylethylamine. J. A. Gunn and M. R. Gurd. 424.
*The Relation of Heart Rate to Intracranial Pressure. O. G. Edholm. 442.
*Observations on the Osmotic Pressure of the Endolymph. P. Aldred, C. S. Hallpike, and A. Ledoux. 446.
The Time Course of Evolution of Oxidative Recovery Heat of Frog's Muscle. D. K. Hill. 454.
The Anaerobic Recovery Heat Production of Frog's Muscle at 0° C. D. K. Hill. 460.
Hydrogen-Ion Concentration Changes in Frog's Muscle Following Activity. D. K. Hill. 467.
Slow Vaginal Potentials. R. B. Bourdillon and O. M. Lidwell. 480.
The Absorption of Water from the Colon of the Rat under Urethane Anæsthesia. B. L. Andrew, J. N. Davidson, and R. C. Garry. 487.
*The Action of Adrenaline upon the Uterus of the Guinea-Pig and Its Modification by Eserine. W. T. Agar. 492.

Blue-Green Region of Spectrum.—The position of the " blue-green " region of the spectrum was found for 100 normal subjects and shown to be less uniform than that of the " yellow " region. (W. M. H.)

Action of Pituitary Extracts on Urine.—A non-pressor but anti-diuretic extract of posterior pituitary lobe, prepared by heating at 99° C. and *p*H 10·0, was found to have no diuretic action on the anæsthetized animal. The diuretic effect of post-pituitary extracts with both principles is therefore due to the pressor activity. From the effects of anæsthesia and operative procedures on urinary osmotic pressure and urine flow it was shown that the anti-diuretic action failed when the urine was hypertonic (freezing value below Δ :—0·800). (W. M. H.)

Amines Related to Adrenaline.—These further studies on amines related to adrenaline show the effect of a double bond in the side chain. Phenylbutenylamine resembles benzedrine in toxicity, action on blood pressure, and effects on smooth muscle. It fails to produce the same restlessness in animals, but a coarse intention tremor becomes marked. Phenylallylamine closely resembles β phenylethylamine in toxicity and actions. In these compounds the introduction of two unsaturated carbon atoms has therefore little effect on physiological activity. The substitution of a phenyl group in dβ diphenyl ethylamine produces a different action—depressant both on C.N.S. and on smooth muscle. (W. M. H.)

Heart Rate and Intracranial Pressure.—The cardiac slowing which occurs when the intracranial pressure rises above systolic pressure was shown in cats to be independent of the rise in blood pressure continuing when such rise was prevented by a mercury valve. (W. M. H.)

Osmotic Pressure of Endolymph.—A method of collecting small quantities of endolymph is described. Measurements of total osmotic pressure show increasing values for blood, c-s-f, perilymph and endolymph in this order. The findings are considered to support the view of a secretory origin of both c-s-f and labyrinthine fluids. It is suggested that endolymph is transferred to the perisaccular connective tissue by excretory activity of the pars intermedia. In the " dilution phase " this connective tissue is distended and the osmotic pressure reduced so that absorption into the blood stream is possible. The wide variations in its bulk and consistency give some support to this theory. (W. M. H.)

Action of Adrenaline on Uterus, and

Modification by Eserine.—Adrenaline applied to guinea-pig uterine muscle which has been soaked for 4–5 hours in Ringer-Locke solution with eserine, causes relaxation followed by contraction. Atropin and ergotoxin do not alter this modification of the normal adrenaline action of inhibition and relaxation. A tentative suggestion is that the production of K in adrenaline inhibition liberates a minute amount of A/Ch, destruction of which is delayed by the eserine. (W. M. H.)

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THE EARLY TREATMENT OF NERVOUS AND MENTAL DISORDERS

W. Lindesay Neustatter

(J. and A. Churchill, Ltd., London. 1940. Pp. 379. 15*s*.)

The value of this book cannot be doubted, crystallizing as it does in its 379 pages an immense amount of practical diagnostic and therapeutic advice. But that it will be thus appreciated by one section for whom it is designed, the general practitioner must rest on a less firm foundation. Specialist knowledge dealing with finer points of diagnostic or therapeutic technique cannot, so to speak, either in this field or elsewhere, " jump the claims of " future generations. It is an error to think otherwise, though it may be done with the very best of intentions. The stream of knowledge is no more an exception to the law of nature than its physical counterpart and coming as it does from many springs must broaden and slow before reaching its *ultima thule*—in this case the practitioner. The specialist in a particular branch must, after all, remain the one who is trained to recognize the earliest stages in the particular disease. It is difficult to see how the process could be easily reversed.

It is a pleasure to note in this agreeably written book, whose title might suggest that it is devoted solely to treatment, that a considerable section deals with early diagnosis. This is an advantage to the reader who might otherwise tend to obtain a lop-sided view of the author's intentions.

Of particular importance is the chapter on " Social and Economic Factors in Disease," in which this Cinderella of medicine is for once taken out of her corner. It is emphasized that until this vast field is explored and some effort made to change such factors a vast breeding ground for disease remains.

One word of criticism. Perhaps too much space is devoted to psychotherapeutic technique, as the reviewer feels that ample literature already exists for those embarking on such troubled seas and that so daring a mariner would hardly limit himself even to precious space devoted to the subject in this small book.

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